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HEREDITARY ATAXIA

Clinical Study Through Six Generations

CAPTAIN JOHN W. SCHUT

MEDICAL CORPS, ARMY OF THE UNITED STATES

THE COPIOUS literature which has arisen on hereditary ataxia has dealt for the most part with small family groups. It follows that a comprehensive picture of the disease could not be expected to emerge from the study of such families, but would be more likely to take form if data from a large family of several generations were available. The series which is the subject of this paper comprises a family derived from a common ancestor and traced in all its branches through six generations. Forty-five of the 342 members are known to have been ataxic, and records of neurologic examination are available on 22. The age of onset of ataxia is known for 32 members, including the 13 still living. The age at death is known for 27 of the 32 who have died, and the duration of ataxia, for 21. The point of particular interest, however, is the diverse manifestations in the clinical features observed within this single family.

CLASSIFICATION

Friedreich,[1] in 1863, was the first to describe in detail a familial form of ataxia. In 1882, when Brousse[2] assembled the cases which had appeared in the literature, Friedreich's ataxia became recognized as a distinct disease. Ladame,[3] in 1890, reviewed the numerous clinical accounts and the 9 autopsy reports of authentic cases. He formulated diagnostic criteria for hereditary spinal ataxia excluding reported cases of ataxia if the age of onset was later than 20 years or if the patellar reflexes were present. Today these two clinical features and pes cavus and kyphoscoliosis are regarded as important signs distinguishing hereditary spinal ataxia (Friedreich's ataxia) from other heredodegenerative diseases.

From the Army Institute of Pathology, Washington, D. C. (25).

This paper is an abridgement of a thesis submitted to the Faculty of the Graduate School of Northwestern University Medical School in partial fulfilment of the requirements for the degree of Master of Science.

1. Friedreich, N.: Ueber degenerative Atrophie der spinalen Hinterstränge, Virchows Arch. f. path. Anat. **26**:391, 1863; **27**:1, 1863.

2. Brousse, A.: De l'ataxie héréditaire (maladie de Friedreich), Thesis, no. 37, Montpellier, 1882.

3. Ladame, P.: Friedreich's Disease, Brain **13**:467, 1890.

Pierre Marie [4] was probably influenced by Ladame's rigid diagnostic criteria for Friedreich's disease when he reviewed a series of reported cases of ataxia and placed them under a new designation "hereditary cerebeller ataxia." Londe,[5] Marie's pupil, added several other cases, and in a lengthy thesis defined the specific clinical features distinguishing hereditary cerebellar ataxia from Friedreich's disease. Londe and other contemporary authors emphasize the following points of differentiation of hereditary cerebellar ataxia and Friedreich's disease: The onset of the former occurred between 20 and 30 years of age, and the disease followed a milder, slower course. The lower extremities were usually involved first, and several years passed before the upper ones became affected. Contractures were often observed, and the deep reflexes were normal or exaggerated. Ocular disorders were varied. ranging from total internal and external ophthalmoplegia with optic nerve atrophy to minor weakness of the external rectus muscle, ptosis and sluggish reaction of the pupils to light. Subjectively, the patients often experienced lancinating pains in the buttocks or loins, but objective sensory loss was less common. The character of the ataxia was said to be cerebellar, and the gait could easily be distinguished from the *marche tabéto-cérébelleuse* of Friedreich's disease. The speech was more indistinct and difficult, whereas in the Friedreich form it was slow, scanning and explosive. The later stages were more frequently marked by mental enfeeblement, but skeletal deformities, such as pes cavus and scoliosis, were conspicuously absent. The disease, which in some instances exhibited regression, was terminated at an advanced age by intercurrent infection, particularly pneumonia. The heredity of the cerebellar form was oftener direct than that of the spinal form.

It was apparent that the type of ataxia which Londe described fitted poorly into the classification of Friedreich's disease in the literature then current. As time passed, numerous reports of cases interpreted as representing transitional forms between the two diseases were published, and led, in the early part of the century, to a controversy as to whether Marie's ataxia was distinct from Friedreich's disease. The predominant view was particularly well expressed by Gordon Holmes,[6] who stated that "neither clinical nor pathological experience justifies its retention as the descriptive title of a form of disease."

There is at present no uniform opinion as to what constitutes the pathologic anatomy of hereditary cerebellar ataxia as defined by Marie.

4. Marie, P.: Sur l'hérédo-ataxie cérébelleuse, Semaine méd. **13**:444, 1893.

5. Londe, P.: Maladies familiales du système nerveux: De l'hérédo-ataxie cérébelleuse, Thesis, no. 158, Paris, 1895.

6. Holmes, G.: An Attempt to Classify Cerebellar Disease, with a Note on Marie's Hereditary Cerebellar Ataxia, Brain **30**:545, 1907.

Guillain, Bertrand and Godet-Guillain[7] described the postmortem observations on a fourth member of the celebrated family initially described (1892) in a clinical report by Klippel and Durante.[8] This member had as the prominent lesion in the spinal cord severe degeneration of the ventral spinocerebellar tract, which was regarded by earlier French authors (Foix and Trétiakoff,[9] Marie and Foix,[10] Marinesco and Trétiakoff[11]) as the essential one in hereditary cerebellar ataxia. Hassin and Harris[12] and Welte,[13] on the other hand, stated the opinion that virtually all forms regarded clinically as hereditary cerebellar ataxia could be classified pathologically as olivopontocerebellar atrophy. Waggoner, Löwenberg and Speicher[14] stated that the changes from case to case are variable and "nonsystemic and that there is no specific patho-anatomic picture in hereditary cerebellar ataxia." They concluded,

> . . . The patho-anatomic picture of heredo-ataxia resembles in some, but by no means in all, cases that of olivopontocerebellar atrophy, since in the former atrophy of the olives and of the pons, or even of the cerebellum, is not a constant factor.

Although no consistent pathologic changes have been found to underlie the syndrome which Marie described, there exists a form of ataxia with preserved deep reflexes occurring after the age of 20 which usually follows a dominant hereditary pattern. In their review of 663 cases of ataxia from the literature, Bell and Carmichael[15] employed the term "spastic ataxia" to denote this form of disease, whereas Sjögren,[16] in

7. Guillain, G.; Bertrand, I., and Godet-Guillain, J.: Étude anatomique d'un cas d'hérédo-ataxie cérébelleuse, Rev. neurol. **73**:609, 1941.

8. Klippel, M., and Durante, G.: Contribution à l'étude des affections nerveuses familiales et héréditaires, Rev. de méd. **12**:745, 1892.

9. Foix, C., and Trétiakoff, C.: Les lésions médullaires au cours de l'hérédo-ataxie cérébelleuse de la maladie de Friedreich et de la paraplégie spastique familiale, Bull. et mém. Soc. méd. d. hôp. de Paris **44**:1140, 1920.

10. Marie, P., and Foix, C.: Lésions médullaires dans quatre cas d'hérédo-ataxie cérébelleuse, Rev. neurol. **27**:797, 1914.

11. Marinesco, G., and Trétiakoff, C.: Étude histopathologique des centres nerveux dans trois cas de maladie de Friedreich, Rev. neurol. **27**:113, 1920.

12. Hassin, G. B., and Harris, T. H.: Olivopontocerebellar Atrophy, Arch. Neurol. & Psychiat. **35**:43 (Jan.) 1936.

13. Welte, E.: Die Atrophie des Systems des Brückenfusses und der unteren Oliven, Arch. f. Psychiat. **109**:649, 1939.

14. Waggoner, R. W.; Löwenberg, K., and Speicher, K. G.: Hereditary Cerebellar Ataxia: Report of a Case and Genetic Study, Arch. Neurol. & Psychiat. **39**:570 (March) 1938.

15. Bell, J., and Carmichael, E. A.: On Hereditary Ataxia and Spastic Paraplegia: The Treasury of Human Inheritance, London, Cambridge University Press, 1939, vol. 5, pt. 3.

16. Sjögren, T.: Klinische und erbbiologische Untersuchungen über die Heredoataxien, Acta psychiat. et neurol., 1943, supp. *27*, p. 1.

his review of ataxia in Sweden, preferred "Pierre Marie's ataxia." In this presentation the term "hereditary cerebellar ataxia" was chosen to designate a similar form of the disease within this family.

A disease of the pyramidal system is sometimes a prominent component of hereditary ataxia, and when it is present the relation to hereditary spastic paraplegia is difficult to assess. Strümpell,[17] who first described the pathologic changes in this disorder, reported moderate degeneration of the spinocerebellar tracts and the posterior funiculus, in addition to a lesion of the pyramidal tract. Certain observers (Raymond [18] Jendrassik,[19] Mollaret [20]) were quick to see the pathologic similarities between spastic paraplegia and both Friedreich's ataxia and hereditary cerebellar ataxia. Most of them were of the opinion that the same pathologic processes underlay all three disorders, the essential difference being in the anatomic localization of the lesions.

The diagnosis of hereditary spastic paraplegia is usually made when a patient shows signs of a severe pyramidal disease with the most prominent manifestations in the lower limbs. Absence of "ataxia" has been regarded as important in distinguishing it from the closely related hereditary disorders. Mason and Rienhoff [21] reported a family the members of which displayed intention tremors of the upper extremities; nevertheless, the general clinical picture still appeared to be compatible with the diagnosis of hereditary spastic paraplegia. Bell and Carmichael,[15] on the other hand, refused to entertain the diagnosis of spastic paraplegia when any "ataxia" was present. They noted that a number of their patients having the essential features of spastic paraplegia on closer examination exhibited decomposition of movement, whereupon they classified the disorder as "spastic ataxia." Of the 46 English families which these authors examined, 45 exhibited hereditary ataxia, and 1, spastic paraplegia. They concluded that "the facts . . . do not appear to justify a discrimination between hereditary spastic ataxia and hereditary spastic paraplegia." The observations of the authors cited raise the question of the coexistence of cerebellar disease in all cases of hereditary spastic paraplegia. It is commonly recognized that a prominent disease of the pyramidal system may obscure certain signs

17. von Strümpell, A.: Ueber die hereditäre spastische Spinalparalyse, Deutsche Ztschr. f. Nervenh. **4**:173, 1893.

18. Raymond, F.: Maladie de Friedreich et hérédo-ataxie cérébelleuse, N. iconog. de la Salpêtrière **18**:5, 1905.

19. Jendrassik, E.: Beiträge zur Kenntnis der hereditären Krankheiten, Deutsche Ztschr. f. Nervenh. **22**:444, 1902.

20. Mollaret, P.: La maladie de Friedreich: Étude physio-clinque, Thesis, Paris, 1929.

21. Mason, V. R., and Rienhoff, W. F.: Hereditary Spastic Paraplegia, Bull. Johns Hopkins Hosp. **31**:215, 1920.

of cerebellar involvement. What appears to be uncomplicated spastic paraplegia in certain stages of the disease may later include cerebellar phenomena. In this series the cerebellar disease was subject to remissions and exacerbations, quite unrelated to the stage of the ataxia, and might have gone undetected in some instances had only a single examination been performed.

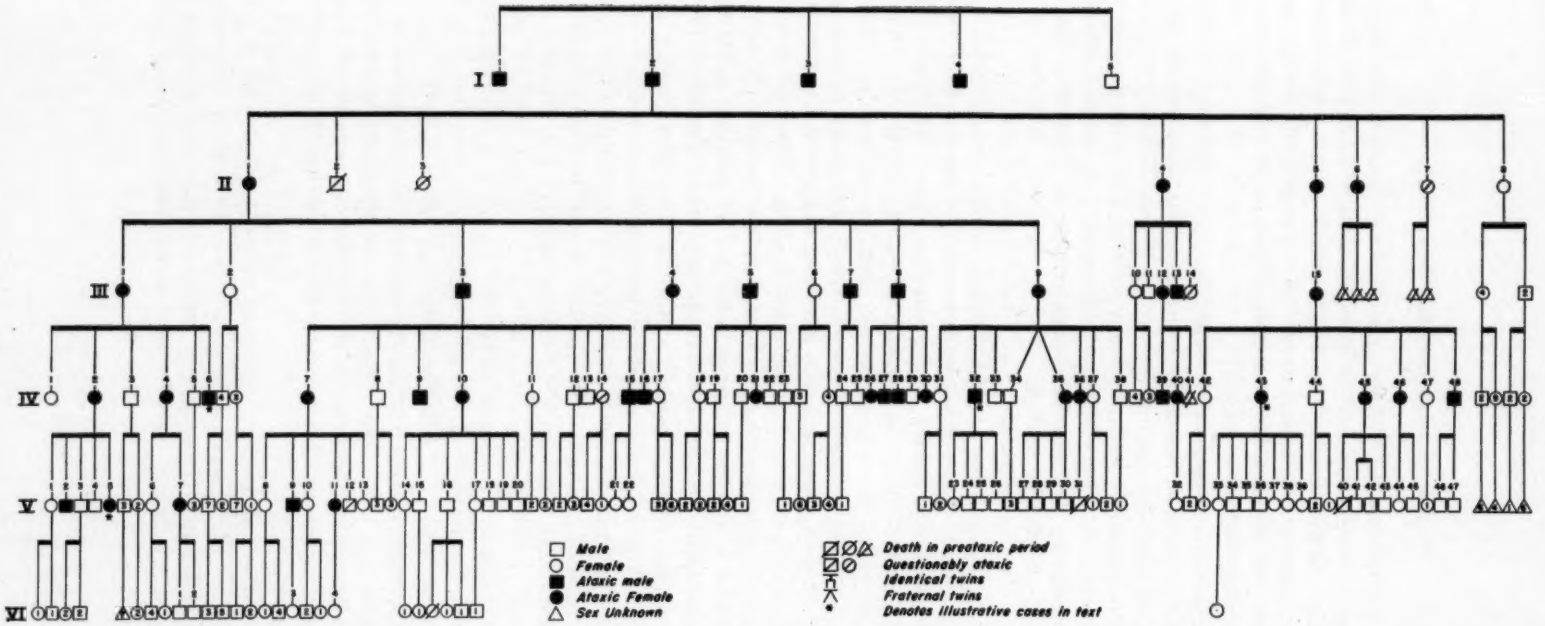
In employing the signs of cerebellar disease to separate hereditary spastic paraplegia from hereditary cerebellar ataxia, consideration must be given the possibility that the former does not exist distinct from the latter. If the diagnosis of spastic paraplegia is allowed in the presence of minimal coordinative disturbances, one can regard it as hereditary ataxia, thereby classifying it with a heredodegeneration, to which it is closely related and undoubtedly belongs.

MATERIAL

The hereditary nature and dominant pattern of the ataxia presented by this family are illustrated in the genealogic chart consisting of 342 members (figure). Ataxia has appeared in 45 members to date. Information concerning the incidence of the ataxia in the members of the first generation was obtained from a son of I-5, who was 80 years of age in 1934. This alert and unusually intelligent old gentleman remarked that, although his father had remained free from the disease, all 4 uncles had staggered during middle age. He had little information concerning I-1, I-3 and I-4, who had remained in the Netherlands, but stated that I-2 had migrated to the United States with some of his daughters in 1866.

The members of generation II consisted of 7 daughters and 1 son, born to I-2. Two (II-2, II-3) died of typhoid in childhood, and 4 (II-1, II-4, II-5, II-6) and possibly a fifth (II-7) became ataxic. Only 3 of these daughters had a part in the transmission of the disease; 2 (II-1, II-5) in the United States and (II-4) in the Netherlands. II-6 was stated to have had "female trouble" and was ataxic, and II-7 died of "tuberculosis of the throat" at 28 years of age; the 5 children born to these two members died in infancy. The details concerning II-4 and her progeny were obtained from IV-1, who visited the Netherlands in 1948, whereas most of the information concerning the other members of generation II was furnished by II-8. This woman, who has subsequently died, was probably the only member of her family who remained unaffected; today her progeny consists of 29 members, none of whom has shown evidence of the disease.

The members of the third generation comprise the progeny of II-1, II-4 and II-5. The 10 ataxic members are dead, but 2 of the 4 unaffected members (III-6 and III-11) are still living. III-6 recalled with reasonable accuracy the ages at onset for most of her ataxic siblings.



Genealogic chart of a family displaying hereditary ataxia. Arabic numerals above symbols are assigned only to members born of an ataxic parent. Children of nonataxic members are indicated collectively by a number within the symbol. A Roman numeral denotes the generation and when followed by an Arabic figure is the member's genealogic number serving as identification. Numbered members and their children who have not reached the age of 35 may yet become ataxic (generation IV-22, 23, 25, 29, 34, 37, 38, 47 and all numbered members of generation V except 1, 3, 4, 8 and 10).

The present study is concerned mainly with the 22 ataxic members of generation IV.[22] Of these 22, 11 are dead, while 11 are living and in various stages of ataxia. Of the 47 children born to the ataxic members of generation III, 17 are regarded as past the age of onset (35 years), while 8 are still under this age.

The members of generation V who are children of the ataxic members of generation IV number 47; for the most part, they are under the age of onset (V-12 through V-47). In certain members of this generation the disease has appeared earlier and in a severer form than in the previous generations; 3 of the 5 ataxic members have already died. However, there is no way of assessing the susceptibility of the unaffected members of this generation, since only 5 have passed the third decade of life.

TABLE 1.—*Distribution of Clinical Types of Ataxia Within The Family Studied*

Disease Form	Criteria Used	Members
Friedreich's disease	(1) Onset before age of 20, (2) absence of deep reflexes, (3) some skeletal deformity	V-5, (V-11?)
Hereditary cerebellar ataxia	(1) Onset after age of 20, (2) presence of deep reflexes	
Subgroup A	(1) Normal or hypoactive deep reflexes, (2) prominent coordinative disturbances	III-7, IV-2, IV-4 IV-6, V-9, V-2, V-7
Subgroup B	(1) Hyperactive deep reflexes, (2) moderate coordinative disturbances	III-8, IV-9, IV-15, IV-16, IV-21, IV-26, IV-27, IV-28, IV-30, IV-32, IV-35, IV-36
Hereditary spastic paraplegia	(1) Early prominent disease of pyramidal system evident in the lower extremities, (2) minimal coordinative disturbances	IV-43, IV-48

Thirteen ataxic members were personally observed by me; the records of 9 other members were obtained from various hospitals where they had been patients, constituting in aggregate the largest series of ataxic descendants of a common ancestor ever assembled. The disease appeared in three forms, which were differentiated by the degree of coordinative defect and the activity of the deep reflexes. The types of ataxia included were Friedreich's disease (hereditary spinal sclerosis), 1 case; hereditary cerebellar ataxia (hereditary cerebellar sclerosis), 19 cases; hereditary spastic paraplegia, 2 cases (table 1). Hereditary cerebellar ataxia was subdivided into a subgroup characterized by normal reflexes and prominent coordinative disturbances, and another, characterized by hyperactive reflexes and moderate signs of cerebellar deficit.

22. A clinical and pathologic study of one member of this generation (IV-27) has been the basis for a previous report (Gray, R. C., and Oliver, C. P.: Marie's Hereditary Cerebellar Ataxia [Olivopontocerebellar Atrophy], Minnesota Med. **24**:327, 1941.)

Each group and subgroup are illustrated by a representative case in the following reports.

REPORT OF CASES

HEREDITARY SPINAL ATAXIA (FRIEDREICH'S DISEASE)

CASE 1 (V-5).—The patient was first seen in 1940, when she was 19 years of age. She then appeared severely ataxic; the onset two years earlier had been marked by unsteadiness in the hands and legs. When examined at the age of 25, she was mute, unable to walk and incontinent. She had been a normal infant, who learned to walk and talk before her time, and she had excelled in school. The menarche had occurred at 13, and menstruation was normal at first but had become irregular and scanty. For some time she had taken nothing but fluids and semisolids, and even these produced epigastric discomfort and flatulence. Poor appetite and difficulty in swallowing were other factors leading to inadequate food intake. She was habitually constipated.

Examination revealed an emaciated woman, who appeared much older than her age of 25. Her height was 66 inches (167.6 cm.) and her weight 80 pounds (36.3 Kg.). The pulse was rapid and thready; the blood pressure was 115 systolic and 70 diastolic. Her face was wizened and immobile, and coarse vertical, parallel wrinkles appeared when she attempted to smile. She was stooped, and her neck was bent far forward because of prominent kyphosis. The skin was smooth, shiny, pale and cool, with moderate cyanosis of the lower extremities. The forehead was low; the hair was red and brittle, and the eyes were sunken in their orbits. She had chronic conjunctivitis and blepharitis. The lips, gums and buccal mucosa were pale; the gums were retracted, but all the teeth were present and without caries. The tongue was smooth and the pharyngeal mucosa red and injected. The pharynx appeared large as a consequence of atrophy of the parafaucial musculature. The breasts were completely atrophied. Except for dorsal kyphosis, no skeletal deformities were noted.

The patient appeared mentally deficient, but it is possible that her motor and speech difficulties interfered with the recognition of her actual mental state. However, in many tests she would not or could not participate correctly.

The pupils were large and equal and reacted to light and in accommodation. All movements of the extraocular muscles were performed, and no nystagmus was noted. Arcus senilis was present bilaterally, and some haziness around the nerve heads was observed on funduscopic examination. Reaction to touch and pinprick over the face was normal, but the facial musculature was weak, and the gag reflex was absent. The patient could not speak audibly but attempted to make herself understood by hoarse whispers. The vocal cords could not be visualized because of poor cooperation. Fasciculation of the tongue was marked. Atonia and atrophy of the entire musculature were striking; however, strength was remarkably well preserved in spite of the degree of wasting. There was no involuntary movement or fasciculation of the musculature.

All the deep reflexes were absent. The plantar response was diminished, and the Babinski sign and related reflexes were not elicited.

Numerous signs indicating severe disease of the cerebellum were noted. There were generalized slowness of movements and prominent ataxia of the trunk and extremities. Her few spontaneous movements were discontinuous and decomposed.

There was slowness in executing movements and dysmetria in the finger to nose test, but no past pointing or intention tremor. The heel to knee test also showed disordered movement. The rebound phenomenon was normal. There was a continual fine oscillation of the head.

Tactile and pain sensibility were everywhere normal, but deep tendon and muscle sensibility were severely affected. Vibratory stimuli were not felt in the malleoli or the radiuses but were faintly perceived on the patella. Muscle and tendon sensibility were so impaired that the patient was unable, when her toes were moved, to judge accurately whether they were flexed or extended.

The patient was cared for at her home until July 24, 1946, when she was admitted to the Fairmount Hospital in Kalamazoo, Mich., with the diagnosis of diphtheria. After eleven days in the hospital she was discharged as improved and was admitted to the County Infirmary. The records there contained no reference to examinations, but a note stated that the patient had "progressive muscular dystrophy, myocardial insufficiency and cerebellar ataxia." Prior to her death, in January 1947, the patient complained continually of being too hot, although the room was kept cooler than was comfortable for her associates.

At autopsy, the brain stem, spinal cord and cerebellum were found to be reduced in size. The posterior columns of the spinal cord were completely demyelinated; the spinocerebellar tracts were also definitely involved. In the medulla and cerebellum there was a typical olivopontocerebellar atrophy with prominent shrinkage and demyelination of the inferior and middle cerebellar peduncles and demyelination of the medullary layer of the cerebellum. The hypoglossal and vagus nerves were degenerated. Further details will appear in a separate report.

Comment.—The diagnosis of hereditary spinal sclerosis (Friedreich's ataxia) was based on the criteria indicated in table 1. The diagnosis for V-11 was probably the same, but in her case no records of examinations were found. She was known to have had pes cavus, and it was said that the onset had occurred before the age of 20 years. These were the only 2 members in the entire series in whom onset occurred before the age of 20.

Unfortunately, no records of examinations performed before 1946 were available for V-5; therefore the status of her deep reflexes in the early stages of the disease is unknown. However, no other member in this series showed disappearance of all deep reflexes in the late stages, although 8 members—one, her mother (IV-2), and another, an uncle (IV-6)—were examined in a similar stage of disability.

Certain members of this family, closely related to V-2 and V-11, had a syndrome resembling hereditary spinal ataxia (Friedreich's ataxia) in that they exhibited normal or diminished deep reflexes with earlier and severer involvement of deep sensibility. This tendency toward diminished reflex activity appeared in all remaining ataxic members of generation V (V-2, V-7 and V-9) and also in IV-2, IV-4, IV-6 and III-7. Because they exhibited this syndrome, they were regarded as belonging to subgroup A under hereditary cerebellar ataxia.

HEREDITARY CEREBELLAR ATAXIA

SUBGROUP A

CASE 2 (IV-6).—A man aged 42 was in the advanced stages of neurologic disease when seen in the summer of 1946. He was unable to give an accurate date of onset of ataxia, but his oldest sister stated that a disturbance of gait became evident when he was 29 or 30 years of age and had been very slowly progressive. He had been confined to his chair continuously for several years, unable to make a purposeful movement. Besides many constitutional symptoms, he complained of difficulty in swallowing and blurring of vision, of uncertain duration and severity. Constipation and bouts of urinary retention with cystitis were treated with neostigmine, with some success. His local physician stated that he often had periods of unmotivated laughter, irritability and stubbornness. He showed poor judgment, minor disorientation in time and paranoid trends.

The patient was asthenic; he was 75½ inches (191.8 cm.) tall and weighed 135 pounds (61.2 Kg.). His pulse was weak and thready, with a rate of 75. His blood pressure was 114 systolic and 74 diastolic. The nail beds were slightly cyanotic; the finger nails were frayed. The fingers tended to take bizarre positions, some being flexed and abducted while others were hyperextended and adducted, especially when the patient's attention was not focused on his hands. Further physical examination revealed some dependent edema of the ankles, brown tropic areas on the shoulders and pronounced dorsal kyphosis.

The pupils were slightly dilated and reacted to light and in accommodation. Nystagmoid movements were noted on lateral gaze, but no rhythmic movements. Funduscopic examination showed the temporal half of the fundus to be paler than the nasal half bilaterally. All movements of the extraocular muscles were performed with ease. The gag reflex was poor and much delayed. There were wavy fasciculations of the tongue, and a coarse tremor with movement, but its strength seemed normal. Of the deep reflexes, the biceps and the patellar were normal and equal on the two sides, but the achilles reflex was absent bilaterally, as were the remaining arm reflexes. The abdominal skin reflexes were difficult to obtain, mainly because of the position in which the patient was examined. The Babinski and other related reflexes or clonus was not elicited. There was generalized wasting of the musculature. Hypotonia was evident, for the extremities often assumed unnatural positions and many parts were abnormally mobile at the joints, especially the fingers, elbows and ankles.

Severe truncal ataxia occurred when the patient leaned forward in his chair. The finger to nose test revealed slowness in initiating movements, with many errors in direction and range. Past pointing or involuntary movements were not observed, but conspicuous dysmetria was demonstrated in spite of the slowness of movement, and there was a slight, terminal, coarse intention tremor of the fingers. The rebound phenomenon of Holmes was present and strongly positive, failing to improve on successive attempts. Rapid alternation of movements was impossible. The patient spoke with a slow, monotonous drawl and much slurring.

Tactile and pain sensibility were normal. There were loss of deep sensibility, as evidenced by the absence of vibratory perception in the ankles and patellas, loss of muscle and tendon sense, and a positive Abadie sign; however, sense of position seemed to be normal in the great toes.

During the year following this examination, the patient survived an attack of pneumonia, a severe acute infection of the upper part of the respiratory tract and several bouts of urinary retention and cystitis. He began to have more difficulty

in swallowing, and his food intake became inadequate. He lost weight and suffered from extreme inanition. He required continual attendance and was unable to lie down or to sleep properly. His skin was always wet and cool. He died suddenly in June 1947.

At autopsy, the brain, cerebellum and spinal cord were found to be reduced in size, especially the cerebellum. In the spinal cord, changes were confined to a small area of the ventral part of the fasciculus gracilus and to the anterior horn cells. In the medulla, the olivary nuclei, and, to a less degree, the pons were affected. The essential pathologic process was in the cerebellum, where the there was a positive Babinski sign bilaterally. There was no clonus, but elicitation and the brachium pontis had not undergone the degree of pathologic change described in case 1, and hence it was difficult to determine whether this case represented a cortical cerebellar atrophy or an olivopontocerebellar atrophy.

Comment.—The classic signs of cerebellar disease characterized the clinical picture in this case. A disease process in the posterior roots and/or the posterior columns, evidenced by the loss of vibratory sense, may have been responsible for the loss of the achilles reflex. The actual time of onset of the disturbance of deep sensibility in this case was not known, but it was late in the course of the disease in IV-2, IV-16, IV-32 and V-9.

The members examined in the initial stages of the disease who presented a normal pattern of reflex activity were III-7, IV-4 and V-7. In these patients the degenerative process in all probability had not yet involved the pyramidal system.

SUBGROUP B

CASE 3 (IV-32).—This patient, the second child of III-9, was 41 years of age when first seen, in June 1946. He had noted incoordinate movements of the hands as the first symptom at the age of 25. The progress of the disease was unremitting, involving his gait and speech, until at the age of 37 he could hardly walk and his speech was almost unintelligible. More recently, retracted eyelids and dilated pupils had produced a staring expression and the appearance of exophthalmos. He had photophobia but no diminution in visual acuity. He found it difficult to cough and swallow fluids, and he complained of hoarseness after talking for a time. Dyspnea was associated with his attacks of epigastric discomfort and flatulence. Constipation was persistent. He had severe urgency, frequency, nocturia and trouble in controlling the stream, with resulting dribbling and incontinence. The patient was irritable and stubborn; his judgment in many things was interpreted as poor, but he seemed alert and interested in his surroundings.

The patient was well nourished and well developed, with an athletic constitution; his height was 72 inches (182.9 cm.) and his weight 200 pounds (90.7 Kg.). The pulse rate was 72, and the blood pressure, 150 systolic and 85 diastolic. His face wore a startled expression; the pupils and eyeballs were prominent. The tongue was smooth; the tonsils were large and cryptic. The fingers tended to take odd positions in relation to one another. There was slight scoliosis of the spine in the upper thoracic region but no other deformities.

The pupils were regular and equal; they were greatly dilated and reacted sluggishly and incompletely to light and poorly in accommodation. All extraocular muscular movements could be performed, and nystagmus was not noted. The

blood vessels of the fundi had a vein to artery ratio of about 3:1, with occasional constrictions in the arterioles. The palpebral fissures were wide. There was a constant coarse fasciculation of the facial musculature, the amplitude of which was increased on grimacing so as almost to constitute a tremor. The periorbital muscles were weak, and he could close his eyes only by distorting his face. The patient was tongue tied; the tongue was small, and attempts to hold it immobile aggravated the fasciculation and the coarse, wavelike tremor.

The deep reflexes were extremely hyperactive in the upper and lower extremities. The abdominal skin and cremasteric reflexes were difficult to elicit, and there was a positive Babinski sign bilaterally. There was no clonus, but elicitation of the reflexes evoked a clonic phenomenon, which lasted about two seconds after the tendon had been struck. There was a moderate amount of spasticity with the cogwheel phenomenon.

It was almost impossible for the patient to walk unaided, but he made some progress by supporting himself on the wall or furniture. In the attempt to walk, the trunk was bent over 90 degrees, and severe ataxia of the trunk and extremities was observed. The supporting musculature displayed a combination of coarse, localized intention tremors and fine, fibrillary, generalized tremors, but no weakness. Lowering the temperature of the room when the patient was reclining produced uncontrollable shivering, made up of both the coarse and the fibrillary tremors.

All voluntary movements were characterized by gross irregularity, with errors of direction, range and rate. In the finger to nose test a slight terminal intention tremor was noted; the other fingers struck the face, for the patient was unable to form a fist. There was a clonic character to the initiation of movements, and a "pulsating" effect could be detected on palpation when a muscle was tensed. Muscular activity appeared seriously disorganized, for the sequence of movements was disturbed. Initiation and relaxation of movements were retarded, but a normal rebound phenomenon could be elicited, and the knee jerks were not pendulous. Rapid movements could not be accomplished. Speech was hesitant, slurring and explosive to the point of unintelligibility. Tactile, pain and deep sensibility were not impaired.

The patient was seen again in April 1948, at the age of 43. His speech had become more intelligible, and he claimed that he was better able to feed himself. He was unable to see distant objects clearly. His disability had not increased, and the results of examination at this time differed from those in the previous one in the following respects: The pupils now failed to respond to light and in accommodation; the movements of the extraocular muscles were limited, especially in upward gaze, and some nystagmoid movements were noted. Fasciculation was not present in the facial muscles, although it was still observed in the tongue; the coarse, wavelike tremor seen at the preceding examination had disappeared. His reflexes had remained the same, but he now had a sustained ankle clonus bilaterally. On palpation of the tensed muscle, no "pulsation" was felt, as in the first examination, and the clonic character of initiating movements had disappeared. All movements were initiated and performed with extreme slowness, with evidence of discontinuity and decomposition, but without conspicuous dysmetria. The coarse terminal intention tremors of the fingers were less evident. In elicitation of the rebound phenomenon, the arm oscillated for some time in a clonic fashion; but as a whole the degree of impairment of activity due to errors of direction and range had decreased. His fingers had become more manageable; they now occupied normal relations to each other, and he was well able to make a fist.

Sporadic involuntary movements of the fingers, especially of the right index fingers, were seen on occasions. He had moderate to severe spasticity, but the cogwheel phenomenon had disappeared. Pain was felt more acutely on the face than the trunk, and vibratory sensibility, moderately diminished, was more acute over the left than the right internal malleolus. The patient's mental status had not deteriorated, for he was cooperative and performed in all tests to the limit of his motor ability.

Comment.—There was an obvious difference between the syndrome in this case (IV-32) and that in case 2 (IV-6). The pyramidal tract was involved in this patient, but there was no evidence of this factor in the syndrome of IV-6, although both patients presented signs of cerebellar dysfunction. The hyperactive deep reflexes and associated signs of pyramidal disease were more prominent in this patient and in IV-28 than in other members of the subgroup. For instance, both IV-28 and IV-32 had a positive Babinski sign, whereas the others had normal plantar responses.

The intensity of the cerebellar and pyramidal components of the disease did not appear constant in any member observed. In IV-32 the pyramidal component had increased during the two years between examinations, whereas the signs of cerebellar disease had diminished.[23] The clinical course of IV-28 furnished another example; this member had a staggering, broad-based gait when examined in 1946, but two years later he presented a shuffling, short-stepped, spastic-ataxic gait, with other signs of advancing pyramidal disease.

SPASTIC PARAPLEGIA

CASE 4 (IV-43).—The patient, a woman aged 43, in 1946, had been aware of subjective symptoms of the ataxia only four years earlier, but her husband had noted slow progression of the present signs for ten years. Involvement of the lower extremities, affecting her gait, antedated the disorders of the upper extremities and speech. Initially she had complained chiefly of unsteadiness and weakness of the ankles and legs and of rapid fatigability. She had recently lost considerable weight. She complained of headaches, constipation and nervousness. Moderate hoarseness and difficulty in swallowing certain foods were late developments. Some incontinence was noted; this may have been related to her obstetric history. She claimed that menstruation was established "artificially" when she was 20 years of age, after which it was accompanied with profuse menorrhagia. A recent bleeding episode had necessitated hysterectomy. She had had seven children and one miscarriage, following her third child.

When examined in 1946, the patient was poorly nourished and wasted. The left leg was smaller than the right, and her face was asymmetric, strained and immobile, with a staring expression. Her height was 65 inches (165.1 cm.), her weight, 100 pounds (45.4 Kg.), her pulse rate, 100, and her blood pressure, 106 systolic and 78 diastolic. She was cooperative and alert. The fingers were held

23. This member received 100 U. S. P. units of crude liver extract each week from January 1948 to the time of the last examination.

in odd positions. No actual deformities were observed, but the cranium was of an unusual shape. The supraorbital ridges were prominent; the ears were flared, and the head was small, with a low forehead.

The pupils were widely dilated and reacted sluggishly to light and poorly in accommodation; hippus was conspicuous. Slight enophthalmos and ptosis were observed, and ocular movements were performed slowly. There was no nystagmus. Funduscopic examination disclosed no abnormalities. A continuous fine fasciculation of the muscles of the left corner of the mouth was present, with definite paresis of the facial musculature, most pronounced on the right. The uvula was large and pendulous and moved properly; the gag reflex was normal. A fine tremor and fasciculation of the tongue were observed.

The deep reflexes were extremely hyperactive throughout. The upper abdominal skin reflexes were sluggish and exhaustible, and the lower abdominal skin reflexes were absent. The Babinski toe sign and related reflexes were elicited. There was bilateral sustained ankle clonus with an unsustained patellar clonus, and moderate plastic rigidity of the muscles was evident. The strength of the muscles of the face and the lower extremities was poor.

When the patient was assisted to stand, it was noted that she had a broad-based stance and stooped posture. All muscles supporting her stance were tense and immobile, and palpation revealed a fine "pulsation"; this condition was present in other muscles when they were held against force. Incoordination of the muscles of the hand and fingers made it difficult for her to form a fist. Speech was drawling, monotonous, hoarse and jerky, with occasional slurring. In this case dysmetria was absent; the finger to nose test was performed with accuracy and rapidity, as was the heel to knee test, and no intention tremors were seen. Rapidly alternating movements were impossible because of increased muscular tone. There was no decomposition of movement or ataxia, and the rebound phenomenon of Holmes was not present.

Two years later the patient's disease had progressed. There was now a constant movement of the muscles of the face, especially above the left eye and at the left corner of the mouth. The paresis of the facial muscles on the right side had become more prominent. An involuntary static tremor of the right thumb, consisting of abduction and adduction, was seen on occasions. The patient was unable to walk alone, but when assisted she walked with a scissors-like gait. The achilles reflex, which was very hyperactive, could not be elicited without evoking a sustained clonus, and the Babinski sign and related reflexes were all present. The finger to nose test revealed a slight intention tremor, which was exaggerated terminally; however, she had no dysmetria or discontinuous or disorganized movements.

Comment.—Two features of this patient's disease differentiated her syndrome from that in the 3 other cases presented: (1) the late appearance of mild coordinative disorder and (2) the initial pyramidal disturbances of the lower extremities. It is probable that this syndrome was common to all the affected members of the sibship of which IV-43 was a member. Examinations could not be made on IV-45 and IV-46, but IV-48, aged 31, had had spastic paraplegia for eight years. Examination showed pyramidal disease, localized to the lower extremities. III-15, the mother of these members, was said to have been paralyzed in the lower extremities without involvement of speech or of the hands.

COMMENT

GENERAL NEUROLOGIC AND GENETIC FEATURES

The ataxia in this pedigree is a dominant hereditary trait, for each of the affected members had one ataxic parent, and the incidence in most family units did not vary significantly from the predicted ratio of 1:1.

Clinical Types and Variations.—In this series, the differences in the clinical pictures of ataxia from member to member permitted a division into three clinical types: Friedreich's disease, hereditary cerebellar ataxia and hereditary spastic paraplegia. This classification was not rigid, and the syndromes overlapped, but typical members of each group had distinctive clinical features, as the case reports emphasize. The members selected to illustrate the divergent forms were in the advanced stages of ataxia; however, most members could be assigned to their respective categories early in the course of the disease, since the pattern of reflex activity, once established, appeared to be subject to little change.

The status of the deep reflexes has been used as a criterion in distinguishing the clinical forms of the disease. Hence, if the course of reflex activity during progress of the disease were subject to unpredictable changes it would not serve as an acceptable criterion. The concept that reflex activity remains essentially the same during the disease is in agreement with the view of Bell and Carmichael,[15] who have observed at least 100 cases of ataxia in England and have reviewed the entire literature on hereditary ataxia. However, it is contrary to the opinion of Waggoner, Löwenberg and Speicher,[14] who stated that reflexes tend to diminish in the late stages, and also to the observations in certain cases reported by Triebel,[24] Morris [25] and Klippel and Durante,[8] who noted the loss of certain deep reflexes in the later stages of ataxia. In this series the loss of the achilles reflex (IV-6, V-9) has been noted; otherwise, reflex activity has not been observed to diminish in the late stages of the ataxia.

The members within each group and subgroup (table 1) were closeiy related. For instance, Friedreich's disease and the syndrome resembling this disease exhibited by all members of subgroup A were confined to the progeny of III-1 and IV-7 (with the exception of III-7). Spastic paraplegia was limited to III-15 and her children. All the members comprising subgroup B lay between these two branches in the genealogic chart (figure) and were first cousins.

24. Triebel, H.: Die Familie K.: Eine Studie über die Vererbung der Friedreichschen Krankheit (hereditären Ataxie), Deutsche Ztschr. f. Nervenh. **75**:111, 1922.

25. Morris, J. N.: Hereditary Cerebellar Ataxia, Internat. M. J. Australia **13**:185, 1908.

To my knowledge, this is the first family in which these three forms have been observed. It is quite possible that if data were obtained on additional branches of other families exhibiting hereditary ataxia a greater variation in the syndrome might have been disclosed.

Age at Onset.—In the early stages of the disease, symptoms evolved insidiously, often intermittently, making it difficult to determine the exact time of onset. Occasionally the first symptoms appeared during pregnancy (V-11) or illness (IV-16), but when no precipitating factor was

TABLE 2.—*Age at Onset for Affected Members of Generations III, IV and V*

Generation	Members in Each Age Group						Total No. of Patients	Number Under Age of Onset	Number Past Age* of Onset
	17-19	20-23	24-27	28-31	32-35	35-40			
III	0	1	2	2	1	1	7	0	4
IV	0	5	6	6	3	0	20	8	17
V	2	1	2	0	0	0	5	36	5

* Upper limit of the age at onset.

TABLE 3.—*Average Age at Onset and Percentage Affected for Generations III, IV and V*

Generation	Total Number* of Members	Number of Ataxic Members	Number for Whom Age at Onset Was Known	Percentage Affected†	Average Age at Onset, Yr.
III	14	10	7	78	29.4
IV	47	22	20	44	26.4
V	46	5	5	38	22.2

* This number does not include any member who died in infancy, or any born of nonataxic members.

† In generations in which all members were past the age of onset, the percentage affected was computed directly; otherwise, it was ascertained through a modified life table.

operative the onset was stated to have occurred within an age range of years; this range was used in all computations regarding age of onset.

The age at onset is known with reasonable accuracy for 32 members. The age range over which the disease made its appearance in all members was from 17 to 35, with the exception of III-5, in whom it was stated to have been between the ages of 35 and 40 (table 2). The average age at onset for the 32 members was 26.5 years, but it varied somewhat from generation to generation, as shown in table 3; this difference was statistically significant.

The tendency for the age of onset to become lower with each succeeding generation has been termed the phenomenon of anticipation. In all ataxic families in the literature this phenomenon has consistently been present; often the age at onset fell rapidly with each succeeding genera-

tion (Vorkastner,[26] Schröder [27]), so that the ataxia disappeared from the stock after two or three generations. These families were small, but when the age of onset was maintained above the reproductive age, larger families were the rule, as in the present series and in those of Neff [28] and Brown.[29]

The average age at onset for 64 patients with ataxia of the type classified as "Pierre Marie's ataxia" by Sjögren [16] was 34; the average age at onset for his 84 patients with Friedreich's disease was about 13 years. In the series of 663 patients with ataxia reviewed by Bell and Carmichael [15] the average age at onset of ataxia of the recessive pattern was 11.7 years for Friedreich's disease and 14.7 years for spastic ataxia; for the dominant pattern, it was more variable and averaged 20.4 years for Friedreich's disease and 36.3 years for spastic ataxia.

Sex Differences.—Comparative data on the affected men and women are summarized in table 4, illustrating the essential differences in the dis-

TABLE 4.—*Comparative Data on Affected Men and Women*

	Women	Men	Total No.
Number affected (total)	25	20	45
Average age at onset, yr.	25.8	27.5	26.5
Number for whom onset is known	18	14	32
Number deceased	18	14	32
Number for whom age at death is known	17	10	27
Average age at death, yr.	35.2	39.6	36.8
Number for whom duration is known	9	12	21
Duration, yr.	9	11.7	10.2
Number with progeny	19	9	28
Total number of children	85	38	123

ease between the sexes. The average age at onset for the 18 affected women in whom it was known to have occurred was about a year and a half less than that for the 14 affected males. The age at death averaged four and a half years less for the women than for the men; however, neither difference was statistically significant. Using only the age at death as an index of severity, Gray and Oliver,[22] in their discussion of certain branches of this family ten years ago, considered the possibility that the disease was severer in women of the family. If the ages of onset and death are correlated with the degree of severity in the present family, it would appear unlikely that the women are more severely affected.

26. Vorkastner, W.: Ueber hereditäre Ataxie, Med. Klin. **10**:360, 404, 448 and 495, 1914.

27. Schröder, W.: Zur Vererbung der Friedreichschen Krankheit, Deutsche Ztschr. f. Nervenh. **142**:221, 1937.

28. Neff, I. H.: A Report of Thirteen Cases of Ataxia in Adults with Hereditary History, Am. J. Insan. **51**:365, 1894.

29. Brown, S.: On Hereditary Ataxy, with a Series of Twenty-One Cases, Brain **15**:250, 1892.

Although a statistically significant difference in the ages of onset and death between men and women could not be demonstrated, certain facts, nevertheless, suggest that the slight differences observed may be of some consequence. Pregnancy seemed to produce exacerbation of the disease in most instances, and at least 2 members (II-1, III-9) died in childbirth or shortly thereafter. Antibiotics prolonged the lives of IV-6 and IV-9 and possibly prevented an early death in the cases of IV-28, IV-32 and IV-48, all males. However, antibiotics have been used in the treatment of only 1 woman (IV-26), without effect.

In spite of the earlier age of onset in women, the total progeny for 19 of the 25 women affected was 85. Only 9 of the 20 affected men had children, and these progeny numbered 38, but it should be remembered that I-1, I-3, and I-4, all affected males, may have had progeny in Netherlands.[30]

Initial Symptoms and Signs.—I have had the opportunity to observe several members of this family during the initial stages of the disease. Usually the patient's siblings or associates realized that ataxia was impending before definite neurologic signs could be elicited or before the patient admitted any symptoms. Although none was able to suggest the exact change that was responsible for this impression, close observation revealed several factors which suggested incipient ataxia. There were generalized poverty of and slowness in initiation of movements; the eyelids, which were slightly retracted, were moved sluggishly and infrequently, and consequently foreign bodies often lodged in the eyes. The patient was often unable to move quickly enough to seize a thrown object, and occasionally an ataxic member would volunteer the information that running had become impossible before the onset of any other recognized symptoms.

Among the earliest manifestations was the change in facial expression, which also preceded other objective evidence of the disease. Serial photographs of some members disclosed that their faces were slowly becoming asymmetric, or sleepy in appearance. Staring eyes, also a component of this altered expression, resulted from a slight retraction of the upper eyelids, infrequent blinking and dilated pupils, simulating exophthalmos. Other early changes in expression could be attributed to diminished tone of the orbicularis oculi muscle, relaxing the wrinkles at the angle of the eye. Shortly after these signs were noted, minor hypermetric errors, lack of associated movements and transient hypotonia appeared.

Regardless of the type of disease, or of what signs indicated incipient ataxia, a disturbance of gait was the commonest early complaint. This

30. A further genetic discussion will appear in the *American Journal of Human Genetics.*

was usually manifested by a dislike for walking in the dark or on ice and a tendency to trip over minor objects. In the majority, the difficulty in walking appeared to be of cerebellar origin, although the first symptoms, whether disturbances in gait or more diffuse manifestations, varied in accordance with the type of clinical picture which emerged and the initial symptoms characteristic of the particular sibship.

Several patients stated that the first symptom of the disease was a disorder of speech. A characteristic monotony, a tendency to prolong vowel sounds and difficulty in pronouncing "d," "t" and "p" were the abnormalities most frequently noted. In these members fasciculation of the tongue was usually an early sign. Coincident with or preceding speech disorders in some ataxic members (e. g., IV- 21, IV-28) was an alteration in the character of the cough.

The mode of onset in members of this series was varied, and this variation is interpreted as evidence of early involvement of diverse structures within the central nervous system. Variability of the initial symptom from member to member was also a feature in the cases of Triebel [24] and Vorkastner [26]; but the onset in members of the families reported by Klippel and Durante,[8] Curschmann [31] and Morris [25] was stereotyped. Those of Klippel and Durante experienced pain in the lumbar and gluteal regions; those of Curschmann complained of giddiness, while patients of Morris consistently noted blurring of vision as a first sign.

Unusual Features and Characteristics of the Ataxia in the Present Family.—The combination of certain unusual signs in some members of this series set the disease apart and distinguished it from ataxia in other families. Exophthalmos, a rare, associated clinical feature, was noted in IV-26, IV-27, IV-28, III-8 and V-2. The abnormal positions occupied by the fingers and the inability to make a fist were noteworthy manifestations in several members and were unique in this family, to judge from the reports in the literature. Also characteristic were the prominence of certain neurologic signs on the right side of the body, the variability in the mode of onset and the facial expression.

Certain of these signs, notably exophthalmos and the exaggeration of signs on the right side, were noted in the family reported by Ten Cate.[32] His family and the one reported here are from the same national stock, and it is possible that they had an identical progenitor, inasmuch as certain members of generation I (I-1, I-3 and I-4) remained in the Netherlands and have not been traced.

31. Curschmann, H.: Zur Kenntnis der hereditären cerebellaren Ataxie, Deutsche Ztschr. f. Nervenh. **75**:224, 1922.

32. Ten Cate, B. F.: Mededeelingen over hérédo-ataxie cérébelleuse, Nederl. tijdschr. v. geneesk. **37**:1069, 1901.

Course.—The chronologic development of ataxia in the members of this family will be more readily comprehended if stages of the disease are arbitrarily defined.

Stage 1: Symptoms of the disease appear intermittently; two or three signs may be present constantly, e.g., fasciculation of the tongue, dysmetric errors or disorder of speech or cough. (The average duration for the 7 patients examined at this stage was two years.)

Stage 2: Signs marking stage 1 progress, and new ones appear. The patient is able to engage gainfully in most occupations. (The average duration for 6 patients examined at this stage was 5.7 years.)

Stage 3: Partial disability prevents the patient from being self supporting but not from walking and attending to his personal needs. (The average duration for 7 patients examined at this stage was eight years.)

TABLE 5.—*Stages* at Which Various Members Were Examined*

	Stage 1	Stage 2	Stage 3	Stage 4
Friedreich's disease	.....	.....	.....	V-5
Hereditary cerebellar ataxia				
Subgroup A	III-7	IV-4	V-2	IV-2, IV-6
	V-7	.....	V-9	V-2
Subgroup B	IV-35, IV-36	IV-21, IV-27	III-8, IV-9	IV-16, IV-26
	IV-16, IV-15	IV-28, IV-35	IV-16, IV-28	IV-22
	IV-30			
Hereditary spastic paraplegia	.....	IV-48	IV-48	IV-43

* See text for definition of stages.

Stage 4: Inability to walk without support necessitates constant attendance. (The average duration for 8 patients examined at this stage was 12.4 years.)

Although many exceptions exist, in general an affected member was no longer able to work after six years and could not walk unassisted after twelve years.

The average age at death of 27 members for whom the date of death was known was 36.8 years (table 4), a figure which is influenced by the early death of IV-4, IV-45, III-4 and III-7. The average duration of illness of 10.2 years for 21 deceased members is shorter than the average duration of 12.4 years for the 8 members who were examined in the fourth stage. Apparently, many are living past the expected ten years, most likely because of careful supervision, use of antibiotics and other modern medical methods.

There was a positive correlation between the age at onset and the duration of the disease. The younger the age at onset, the shorter the duration of the disease. V-5 (case 1) represents the most severely affected member of this series; onset was at the age of 17 and death at the age of 25. On the other hand, IV-9 had the mildest form of ataxia

of the members examined; although he lived twenty-two years after the onset, he never attained the disability incident to the fourth stage of the disease. The untimely deaths of 4 members (IV-4, IV-45, III-4 and III-7) were apparently unrelated to the severity of the disease, but a history of the mode of death suggests that early bulbar involvement was present in all but IV-45.

In reviewing the records of the various examinations, it was noted that certain neurologic signs characterized the early stages of the disease, while other signs seemed to be late manifestations. Table 6 was drawn up in an attempt to determine the correlation between the twenty-five most significant signs and the stage to which the disease had progressed. The records of all neurologic examinations were analyzed to obtain these data. Seventeen patients were examined at one stage; 4 members, at two stages (IV-28, IV-35, IV-45, V-2), and 1, at three stages (IV-16).

The signs most frequently observed in stage 1 were disturbances of gait and speech and fasciculation of the tongue. Ataxia demonstrated in the finger to nose test with minor dysmetric errors was fairly constant, but other early cerebellar signs were not. Signs implicating the facial nerve were almost as common as fasciculation of the tongue, whereas a change in the character of the cough was noted more frequently than table 6 would indicate. Few new neurologic signs were observed in members at stage 2, but the signs noted in stage 1 were present with greater consistency. A Babinski sign, not present in any patient in stage 1, appeared in 2 members of subgroup B examined in stage 2, and a sluggish pupillary response to light was also noted in 2 siblings (IV-27, IV-28). Stages 3 and 4 were characterized by the appearance of optic nerve and muscular atrophy, static tremors and disturbance in deep sensibility, along with signs indicating increased involvement of the structure implicated in the earlier stages.

Table 6 also shows the consistency with which cerebellar signs were noted. In most members these early signs were soon altered by disease of the pyramidal system. A change from cerebellar hypotonia to normal tone was observed in 2 patients (IV-21, IV-35). In others it was not evident that the pyramidal system became subsequently involved (IV-6, V-5), whereas pyramidal disease did not relent in those in whom it had become established early in the disease. IV-16 may have been an exception, for early spasticity was replaced by atonicity in the later stages; this phenomenon has not been observed in other members. This loss of tone was probably on the basis of a lesion of the lower motor neuron, for both generalized fasciculation and wasting were prominent clinical features in this patient. The recent appearance of an intention tremor in the upper extremities of IV-40, whose disease has been diagnosed as spastic paraplegia, possibly indicates that cerebellar involvement is taking place late in stage 4.

TABLE 6.—*Frequency of Twenty-Five Neurologic Signs in the Four Stages of Ataxia* *

	Stage 1†			Stage 2			Stage 3			Stage 4		
	Present	Absent	No Record	Present	Absent	No Record	Present	Absent	No Record	Present	Absent	No Record
Dysmetria	3	1	3	4	2	0	4	1	2	3	1	3
Adiadokokinesis‡	1	4	2	0	6	0	4	2	1	2	0	4
Hypotonia	1	4	2	1	5	0	1	2	4	3	3	2
Finger to nose ataxia	4	2	1	6	0	0	4	1	2	5	1	2
Rebound phenomenon	2	2	3	2	3	1	3	2	2	1	2	5
Decomposition of movements	0	4	3	0	4	2	2	2	3	4	1	3
Nystagmus	1	4	2	3	2	1	5	2	0	3	3	2
Speech disorder	5	0	2	6	1	0	5	0	1	7	0	1
Optic nerve atrophy	0	5	2	0	6	0	3	3	1	3 + 1†	2	2
Dilated pupils	2	3	2	4	1	1	3	1	3	6	0	2
Poor or absent pupillary response	0	6	1	2	4	0	1	4	2	3	3	2
Partial ptosis	3	2	2	3	1	2	2	1	4	3	0	5
Facial nerve involvement	4	1	2	3	1	2	2	1	4	3	0	5
Difficulty in coughing and/or swallowing	0	3	4	4	2	0	5	1	1	7	0	1
Fasciculation and/or atrophy of tongue	5	1	1	3	0	3	5	2	0	5	0	3
Hyperactive deep reflexes	4	2	1	5	1	0	5	2	0	3	4	1
Babinski sign	0	6	1	2	4	0	2	4	1	2	3	3
Ankle clonus	0	5	2	0	6	0	0	5	2	2	2	4
Romberg sign	2	3	2	4	1	1	5	1	1	..	..	..
Disturbance of deep sensibility	0	4	3	0	6	0	2	3	2	5	1	2
Disturbance of superficial sensibility	0	5	2	1	5	0	2	3	2	3	4	1
Skeletal deformity	1	4	2	1	4	1	0	5	2	3	3	2
Muscular atrophy	0	6	1	0	5	1	4	2	1	6	1	1
Tremor at rest	0	7	0	0	5	1	3	4	0	5	3	0
Mental disorder	0	5	2	1	5	0	2	3	2	3	4	1
Number of patients		7			6			7			8	
Average duration of the disease		2 years			5.7 years			8 years			12.4 years	

* This table should not be used for the determination of frequencies, for certain patients were observed in more than one stage.
† See text for definition of stages.
‡ Adiadokokinesis was not recorded for patients with muscular spasticity.

There was little objective evidence that the disease was remittent, even though most patients were aware that it was not steadily progressive. The intermittent character of the disease was more evident in the initial stages, when an affected member (e. g., IV-30) might appear entirely free from symptoms of the disease at one time (August 1948), and might be ataxic at another (April 1948). The disease appeared to have a more intermittent character in some branches of the family (e. g., that of IV-30) than in others. Infections of the upper part of the respiratory tract caused an exacerbation of symptoms and neurologic signs, followed by a short period of incomplete improvement, in the majority of patients. Strenuous activity and dietary indiscretions were less likely to affect the course of the disease.

The immediate cause of death was most often pneumonia, mentioned by Londe [5] as an important cause of death in hereditary cerebellar ataxia. The mode of death of many of these members, however, suggested that a prominent cardiobulbar disorder appearing late in the course of the disease influenced the exact time of death. Guillain and Mollaret [33] have recently suggested a similar disorder as the cause of death in Friedreich's disease.

SPECIFIC NEUROLOGIC SIGNS

The twenty-five neurologic signs which were listed in relation to the stage of ataxia in table 6 were arranged in table 7 to show the frequency with which they were observed in the clinical types of hereditary ataxia characteristic of this family. The figures in this table are naturally influenced by the stage or stages in which the patients were examined. For instance, the absence of decomposition of movement in 4 members of subgroup B is attributable to the fact that a greater number of patients in this subgroup were examined in stage 1 (table 5), when this sign had seldom become apparent.

The authors, cited in the comparative analysis which follows, have reported families in which there was ataxia of a similar dominant hereditary pattern. Only those reports which include neurologic examinations on members in two generations or more were selected for this review.

Optic Nerve.—Visual acuity was diminished in 3 members (IV-16, IV-6, V-2); pallor of the temporal area of the fundus was observed in the same patients and also in V-9, whose visual acuity was unchanged. The fields of vision were constricted in 2 of the patients with diminished visual acuity and pallor (V-16, V-2). The optic disk of 1 member (V-5) was

33. Guillain, G., and Mollaret, P.: Le syndrome cardio-bulbaire de la maladie de Friedreich: Une des causes fréquentes de la mort dans cette affection, Presse méd. **40**:1621, 1932.

TABLE 7.—*Frequency of Twenty-Five Neurologic Signs in 22 Patients in the Four Clinical Groups*

	Friedreich's Ataxia			Hereditary Cerebellar Ataxia						Hereditary Spastic Paraplegia			Total		
				Subgroup A			Subgroup B								
	Present	Absent	No Record	Present	Absent	No Record	Present	Absent	No Record	Present	Absent	No Record	Present	Absent	No Record
Dysmetria	1	0	0	5	0	2	7	2	3	0	2	0	13	4	5
Adiadokokinesis*	1	0	0	3	2	2	3	5	3	0	1	0	7	8	5
Hypotonia	1	0	0	1	3	3	3	6	3	0	2	0	5	11	6
Finger to nose ataxia	0	1	0	6	1	0	9	1	2	1	1	0	16	4	2
Rebound phenomenon	0	1	0	3	1	3	5	3	4	0	2	0	8	7	6
Decomposition of movements	1	0	0	1	2	4	3	4	5	0	2	0	5	9	8
Nystagmus	0	1	0	5	0	2	7	4	1	0	2	0	12	7	3
Speech disorder	1	0	0	5	0	2	10	0	2	1	1	0	17	1	4
Optic nerve atrophy	?	0	0	3	3	1	1	8	3	0	2	0	4 + 1?	13	4
Dilated pupils	1	0	0	6	1	0	4	4	4	1	1	0	12	6	4
Poor or no pupillary response	0	1	0	1	5	1	3	6	3	1	1	0	5	13	4
Partial ptosis	1	0	0	2	1	4	5	2	5	0	2	0	8	5	9
Involvement of facial nerve	1	0	0	6	1	0	6	5	1	2	0	0	15	6	1
Difficulty in coughing and/or in swallowing	1	0	0	4	1	2	9	1	2	1	1	0	15	3	4
Fasciculation and/or atrophy of tongue	1	0	0	3	2	2	10	1	1	2	0	0	16	3	3
Hyperactive deep reflexes	0	1	0	0	7	0	12	0	0	2	0	0	14	8	0
Babinski sign	0	1	0	1	6	0	3	7	2	1	1	0	5	15	2
Ankle clonus	0	1	0	0	6	1	1	8	3	1	1	0	2	16	4
Romberg sign	0	0	0	3	1	1	7	2	1	0	1	0	10	4	2
Disturbance of superficial sensibility	0	1	0	3	4	0	2	6	4	0	2	0	5	13	4
Disturbance of deep sensibility	1	0	0	3	3	1	2	6	4	0	2	0	6	11	5
Skeletal deformity	1	0	0	3	2	2	1	8	3	0	2	0	5	12	5
Muscular atrophy	1	0	0	3	4	0	3	6	3	2	0	0	9	10	3
Tremor at rest	1	0	0	3	4	0	2	10	0	1	1	0	7	15	0
Mental disorder	0	1	0	3	2	2	1	9	2	0	2	0	4	14	4

* Adiadokokinesis was not recorded in those with muscular spasticity.

indistinct. The incidence of optic nerve atrophy was higher in subgroup A, having been noted in 3 of 7 members, whereas it was observed in only 1 of 8 members in subgroup B.

This mild degree of involvement of the optic nerve late in the course of the disease was similar to that in the cases of Bergman [34] and Neff,[28] but it was not comparable to the total internal and external ophthalmoplegia described by Brown [29] and Morris [25] in some of their cases. Sjögren [16] reported optic nerve atrophy in 34 per cent of his cases of Friedreich's ataxia and in 61 per cent of his cases of hereditary cerebellar (Marie's) ataxia. Londe [5] and Marie [4] stated that optic nerve atrophy was more frequent in hereditary cerebellar ataxia than in Friedreich's disease, and Davison and Wechsler [35] regarded it as a useful sign in distinguishing hereditary cerebellar ataxia from olivopontocerebellar atrophy, since it was less frequent in the latter. In the present series the group in which the disease most closely resembled Friedreich's ataxia was the one (subgroup A) exhibiting the greatest incidence of optic nerve atrophy.

Extraocular Muscles.—Partial ptosis was observed in 8 members, and dilated pupils were noted in 12; both were common signs early in the disease. The nerves to the extrinsic ocular muscles, however, were not commonly affected. Paresis of upward gaze with limitation of other ocular movements was observed in 2 members (IV-32, V-2). V-2 had had paresis of the right rectus muscle from youth, and this became bilateral in the course of the disease. Paresis of the same muscle is present in V-16, who is still under the age of onset. In the literature there are numerous references to involvement of the nerves to these muscles, often in combination with optic nerve atrophy. Brüggendieck [36] reported a case in which there was involvement of all the components of the oculomotor nerve.

Pupillary Response.—Failure of the pupillary response to light was observed in 3 members (IV-27, IV-32 and V-2). Pupils which reacted sluggishly and incompletely to light were observed in 2 (IV-43, IV-28), a phenomenon noted by Walter and Roese [37] and Josephy [38] in their

34. Bergman, W.: Studies in Heredo-Ataxia, Upsala läkaref. förh. **26:1**, 1921.

35. Davison, C., and Wechsler, I. S.: Olivo-Pontocerebellar Atrophy and Unilateral Involvement of Cranial Nerve Nuclei, J. Nerv. & Ment. Dis. **88:**569, 1938.

36. Brüggendieck, H.: Familiäre Hinterstrangerkrankung in drei Generationen, Arch. f. Psychiat. **66:**728, 1922.

37. Walter, F. K., and Roese, H. F.: Ein Beitrag zur Kenntnis der hereditären Ataxie (Friedreich-Nonne-Marie), Deutsche Ztschr. f. Nervenh. **92:**8, 1926.

38. Josephy, H.: Über die hereditäre Ataxie, Deutsche Ztschr. f. Nervenh. **130:**96, 1933.

cases. Unequal pupils, noted only in IV-48, were reported in the cases of Vorkastner,[26] Ten Cate,[32] and Voisin and Macé de Lépinay.[39] Dercum [40] reported a pupillary abnormality which he termed "a reversed Argyll Robertson pupil."

Facial Nerve.—Involvement of the facial nerve, one of the most frequent neurologic signs encountered, was present in 15 members. Commonly it was demonstrated by facial paresis on the right (IV-2, IV-4, IV-43, IV-48); uncommonly, on the left (IV-15). Fasciculation of the facial muscles was a more frequent indication of the involvement of this nerve (IV-6, IV-16, IV-28, IV-32, IV-35, IV-43, V-2, V-7). Weakness of the facial muscles was of early appearance in practically all members and was related to changes of expression. The progressive atrophy of the facial muscles involved the orbicularis oculi most severely, as illustrated in the case of IV-32, who experienced difficulty in closing his eyes. Later in the course of the disease the bony eminences of the face become more prominent (IV-32, V-2), and asymmetries become more pronounced (IV-43, IV-2). The platysma muscle could rarely be demonstrated by grimacing in any stage, but if it could be, some degree of weakness or tremor was always perceptible.

Acoustic Nerve.—Impairment of hearing was noted in 2 members (IV-16, IV-48), and giddiness and dizziness were complaints of IV-16. Deafness was reported late in the course of the ataxia by Sjögren [16] and Klippel and Durante.[8] Giddiness was mentioned as an initial symptom by Triebel [24] and Curschmann.[21]

Glossopharyngeal and Vagus Nerves.—The glossopharyngeal and/or vagus nerves were affected in 15 of 18 members. Some members regarded difficulty in cough and change in character of the cough as early and indicative signs of ataxia (IV-21, IV-28). However, difficulty in swallowing seldom appeared in the early stages, and other signs indicating a disease of these nerves were varied: Hoarseness after talking for some time was a complaint of IV-32 and IV-43; others experienced difficulty in speaking and/or coughing. IV-4 had a pulse rate of 114 one month prior to her death, attributed to "heart trouble following pneumonia." Evidence of the severest involvement was present in V-5, who was mute and unable to swallow solids, and whose examination disclosed atrophy of the parafaucial musculature. The severity of this disturbance was similar to the cases of Dercum [40] and Voisin and Macé de Lépinay,[39] whereas most members of this series could be compared with the patients of Triebel [24] and Brown,[29] who experienced difficulty in swallowing in the late stages of ataxia.

39. Voisin, R., and Macé de Lépinay, M.: Cinq cas d'hérédo-ataxie cérébelleuse dans la même famille, Rev. neurol. **15**:512, 1907.

40. Dercum, F. X.: A Case of Heredocerebellar Ataxia (?) Presenting Unique Features: Reversed Argyll Robertson Pupil, New York M. J. **106**:346, 1917.

Hypoglossal Nerve.—Fasciculation of the tongue was one of the early signs; it was known to have been present in 16 members and was observed in all members whom I examined except IV-21 and V-9. Occasionally a coarse, wavy intention tremor was also seen, especially when the tongue was protruded and an attempt made to hold it steady. Atrophy of the right side of the tongue was noted in 2 members (IV-21, IV-27) and of the left side in 1 (V-2). Triebel [24] and Bergman [34] mentioned "fibrillation" of the tongue in some of their patients. It is of interest that Friedreich [1] noted "tremors of the tongue" in association with degeneration of the hypoglossal nerve.

Involvement of the facial, glossopharyngeal, vagus and hypoglossal nerves of such frequency and severity has not been reported in any other ataxic family. Judging from the initial symptoms encountered, these cranial nerves are the seat of severer involvement than the cerebellum itself. Sjögren's figures show that in hereditary cerebellar ataxia there is somewhat greater incidence of signs referable to the cranial nerves than in the spinal form of the disease.

Muscular Atrophy.—Muscular atrophy, present in 9 of 19 cases, was limited to members in the last two stages of ataxia (table 6). Localized atrophy of the shoulders was present in 3 members (III-8, IV-48, V-2). Later in the course of the disease V-2 exhibited atrophy of the interosseous muscles and forearms similar to that of his mother IV-2, in whom it was more pronounced on the right side. A more generalized muscular wasting was present in 4 members (IV-6, IV-16, IV-43, V-5) and was occasionally associated with transient fasciculation (IV-16, IV-43). Generalized muscular twitchings without atrophy were observed early in III-7 and IV-16 and late in the course of the disease in IV-32.

Involvement of the lower motor neuron in hereditary ataxia often affects isolated groups of muscles and is usually transmitted through the family. Most commonly affected are the muscles supplied by the ulnar and peroneal nerves, and occasionally the muscles of the upper arm and the shoulder girdle are involved, as in this series and in the cases of Bergman [34] and Ten Cate.[32] Sjögren,[16] from his review of ataxia in Sweden, concluded that muscular atrophies were common signs in the late stages of both forms of hereditary ataxia, especially the Friedreich type.

Cerebellum.—Of the 22 members examined, all except 1 (IV-48) showed some signs of cerebellar deficit. Cerebellar dysfunction was more prominent in members of subgroup A than in those of subgroup B, and was absent in the 2 cases of hereditary spastic paraplegia until a coarse terminal intention tremor was recently noted in IV-43.

Most signs of cerebellar involvement detected in the early stages of ataxia could be interpreted as disturbances of the rate of the components of movement; these included slowness of movements, especially in ini-

tiating them, hypermetria and the coarse terminal intention tremor of the fingers. According to Holmes,[41] hypermetria is due to delay in the deceleration of movement, whereas intention tremors result from irregularity in deceleration, and both are evidence of the loss of the particular cerebellar function which influences velocity of the various components of movement.

Hypotonia was independent of disturbances of rate but greatly influenced the degree to which they were manifest. For example, in IV-6, in whom muscular atonicity existed, slowness of movement, dysmetria and intention tremors were prominent. As a rule, however, hypotonia appeared as a transient phenomenon in the early stages, probably influenced by the coincident pyramidal disease in these patients (IV-21). In these instances it was observed that when the tone had apparently returned to normal, the dysmetria, the intention tremors and the other disturbances in the rate of movements were less conspicuous. Hypotonia was occasionally associated with hyperactive reflexes (IV-35), and in this event the patellar reflexes were often pendulous (IV-9, IV-21). The infrequent listing of hypotonia in tables 6 and 7 is misleading because it was a transient sign; furthermore, the atonicity in the later stages may not have resulted from the cerebellar disease.

Holmes [41] stated the opinion that factors other than retardation of the initial phase of movement contributed to adiadokokinesis. In members of this series obvious difficulty in rapidly pronating and supinating the hands seldom appeared in the first two stages, although several tests (square tracing, place running and seizing thrown objects) showed that movements were initiated slowly. Both decomposition of movement and adiadokokinesis, which were more frequent in the late stages of ataxia, are evidence of extension of the same disturbance of movement to proximal segments of the limbs, causing defective postural fixation.

Lack of associated movements was regarded by Holmes [41] as a cerebellar sign unrelated to the others, appearing as an enduring sign in minor lesions of the cerebellum. The exact frequency with which it occurred in this series is unknown, but it was observed accompanying other early cerebellar signs in members IV-21, IV-28 and IV-36.

Early disturbances of gait were the commonest cerebellar signs and led to unsteadiness, staggering and uncertainty in walking, with aggravation of the difficulty in the dark. Since impaired gait was coupled with other signs of cerebellar involvement in the same patient, and since signs referable to the posterior columns characteristically appeared late in the course of the disease, gait of this type was regarded as evidence of involvement of the cerebellum and/or its pathways. The broad-based gait with dysmetric steps which is characteristic of pure cerebellar syndromes was present in only 4 of the members examined (IV-21, IV-35,

41. Holmes, G.: The Cerebellum of Man, Brain **62**:1, 1939.

IV-28 and V-9). The spastic-ataxic gait of IV-28 (as seen in 1948) resembled that described by Bergman [34]; but titubation described by Curschmann [31] was recorded in only 1 case in this series (IV-9), and reeling, noted by Voisin and Macé de Lépinay [39] and by Classen,[42] was not observed in this family. III-4 was stated to have had no disorder in gait.

Disturbances of speech in certain cases could be attributed to involvement of the vagus and hypoglossal nerves; in others the cerebellum or inferior olivary nucleus was implicated. In members whose speech disorder was coincident with a change in the character of the cough, fasciculation of the tongue or other signs referable to the cranial nerves, the disturbance was probably bulbar, and speech became an indistinct drawl in the end stages (IV-16, IV-26, IV-27). In those members in whom swallowing and coughing were unimpaired and the cranial nerves were normal (IV-21, IV-35), speech tended to be slurred or scanning, slow, monotonous and occasionally explosive; this was most likely due to disease of the cerebellum or the inferior olivary nucleus. In the early stages the speech tended to be of one type or the other, but in the later stages the disordered speech was the consequence of degeneration of both these structures. One member of this family was entirely mute (V-5), like the patient with Friedreich's disease reported by Barrett.[43] A disorder of speech was present in all affected members of the present family except IV-48; it was also mentioned by all authors whose works have been reviewed, with the exception of Curschmann [31] and Schröder.[27]

Nystagmus was noted in 12 of 19 patients; 5 of these were members of subgroup A. Horizontal nystagmus was present in IV-16, IV-21, IV-26, IV-9 and V-2; IV-35 and V-7 exhibited vertical nystagmus also, as did V-20, a child under the age of onset for ataxia. The irregular oscillations of the eyes in IV-4, IV-6, IV-28, IV-32 and V-9 were interpreted as nystagmoid movements. Nystagmus was commonly encountered in members of ataxic families reported in the literature; the cases of Triebel [24] are noteworthy, since nystagmus appeared in all members examined and, as in the present family, was often transmitted as a trait distinct from the ataxia, appearing in some nonataxic members. Curschmann [31] noted marked horizontal and vertical nystagmus as an early manifestation of ataxia in his case. Sjögren [16] noted nystagmus in 5 of 25 cases of hereditary cerebellar ataxia and in 56 of 73 cases of Friedreich's disease.

42. Classen, K.: Ueber familiäre Kleinhirnataxie, Centralbl. f. inn. Med. **19**:1209, 1898.

43. Barrett, T. M.: Friedreich's Ataxia: Clinical and Postmortem Study of Two Cases in Brothers at Different Stages of Disease, Arch. Neurol. & Psychiat. **17**:28 (Jan.) 1927.

Tremor at Rest.—Static tremors were noted in 8 members of this series, but appeared in only 2 members prior to stage 4. Static tremors of the fingers and face were apparent in IV-32 and IV-43; a peculiar involuntary sniffing movement of the face was an unusual feature of the disease in IV-32 and V-9. A coarse tremor of the trunk was observed in IV-2, and also in her son V-2 in a similar stage of the disease. Nodding movements of the head were present in III-8 and V-5 in the late stages of the disease. IV-27, the son of III-8, was without evidence of this sign when he was examined, but was known to have exhibited it later. A similar phenomenon was recorded in the cases of Brüggendieck,[36] Vorkastner,[26] Morris [25] and Keiller.[44] Choreiform movements reported by Classen.[42] Vorkastner,[26] Ten Cate,[32] Klippel and Durante,[8] Morris [25] and Brown [29] and athetoid movements noted by Dercum [40] and Josephy [38] were not observed in this series.

Superficial Sensibility.—There were 5 members in whom a disturbance of superficial sensation was noted. Diminished sensation to pinprick below the neck was demonstrated in IV-32, V-9 and IV-16. Both IV-2 and her sister IV-4 had loss of tactile sensation below the knees on the right side. Subjective somatic pain was not a complaint of any ataxic member of this series, but has been reported in the cases of Walter and Roese,[37] Klippel and Durante,[8] Triebel [24] and Brüggendieck.[36] Prominent lumbar and gluteal pain at the onset of ataxia, followed by anesthesia in scattered areas on the lower extremities, was peculiar to the cases of Klippel and Durante.[8]

Deep Sensibility.—Loss or diminution of vibratory sensibility and/or loss of joint sense was present in 6 members examined in the late stages of their disease. In IV-6 and V-5 vibratory sensibility was lost on the external malleoli; in IV-32 and V-9 it was diminished. In all but IV-6 vibration was perceived on the patella; in all but V-5, on the radiuses. V-5 and her mother, IV-2, were the only members having an accompanying disturbance in sense of position, except possibly IV-16, who was stated to have lost muscle and tendon sensibility.

The severest disturbance of deep sensibility was demonstrated in V-5, associated with the loss of all deep reflexes. When compared with the other groups, the disturbance of deep sensibility was significantly earlier, severer and more frequent in members of subgroup A, who were closely related to V-5 and whose reflexes were hypoactive or normal. This indicates that the posterior columns and/or posterior roots, responsible for the integrity of deep sensibility and deep reflex activity, were preferentially affected in members of subgroup A, consisting principally of the progeny of III-1. The degenerative process in these structures

44. Keiller, W.: Four Cases of Olivopontocerebellar Atrophy Giving History of Heredity with Three Autopsies, South. M. J. **19**:518, 1926.

may effect a disappearance of certain deep reflexes if segments of the spinal cord responsible for them become involved. This was probably the course of events in IV-2, IV-6 and V-9, who lost their achilles reflexes, and in the cases of Klippel and Durante,[8] Triebel [24] and Morris,[25] in which certain deep reflexes were lost in the late stages of the disease. Sjögren [16] stated the opinion that 3 of his patients with absence of deep reflexes demonstrated hereditary cerebellar ataxia and that 12 patients with preserved deep reflexes had Friedreich's disease. Bell and Carmichael [15] used the presence or absence of the patellar reflex as the sole criterion in separating hereditary spinal (Friedreich's) ataxia from spastic ataxia.

Pyramidal System.—Pyramidal disease, as evidenced by hyperactive deep reflexes, a Babinski sign and ankle clonus, was present in 15 members of this series. Hyperactive deep reflexes have not been observed to diminish and are present early in the disease, and in some instances in the preataxic period (IV-28, IV-30). Certain members without ataxia nevertheless had hyperactive reflexes (IV-11, IV-12). A Babinski sign was present bilaterally in IV-32 and IV-43; it was limited to the right side in IV-28 and V-2. It was associated with clonus in IV-32 and IV-43 and with normal reflexes in V-2. Members IV-32 and IV-43 had a moderate amount of plastic rigidity.

IV-32 and IV-43 were the only members having a bilateral Babinski sign, ankle clonus and spasticity, but IV-32 had, in addition, signs of a severe cerebellar lesion, whereas IV-43 did not. Signs of pyramidal involvement were localized to the lower extremities in IV-48 and were particularly severe in IV-43, both members whose disease was diagnosed as hereditary spastic paraplegia. As table 7 indicates, all signs of cerebellar deficit are significantly less numerous in these 2 patients.

The Autonomic Nervous System.—Mild exophthalmos, dilated pupils and retraction of the upper eyelids were partially responsible for the startled expression of some of these ataxic patients (IV-26, IV-27, IV-32, V-2, V-7). Usually the same patients displayed tachycardia, constipation and pale, moist, cool skin. The pulse rate was especially high during acute febrile episodes, when it demonstrated unusual rises which did not closely parallel increases in temperature (IV-28, IV-46).

III-8 and his children IV-26, IV-27 and IV-28, as well as IV-21 and V-2, exhibited mild exophthalmos, but although III-3 was said to have had this sign it was not noted in any of his ataxic children. Exophthalmos was noted in the cases of Ten Cate [32] and in those of Yang, Ling and Chang.[45] It is rather uncommon, but is a definite part of the clinical picture of some ataxic patients.

45. Yang, C.; Ling, M. Y., and Chang, S.: Hereditary Ataxia: Familial Occurrence in Five Generations, Chinese M. J. **53**:161, 1938.

IV-28 is subject to periodic attacks suggesting a mass sympathetic reaction, and at present they are a particularly distressing component of his disease; they may, however, have a functional basis. Excessive perspiration at intervals was noted in the histories of IV-32 and V-9; IV-20, a nonataxic member past the age of onset, complains of a similar disorder.

Mental Disorder.—The frequency of mental signs could not be assessed with accuracy, for the sleepy expression led to faulty impressions, while the disturbances of movement interfered with tests used to ascertain the actual intellectual capacity. Only 2 members are known to have had mental changes associated with the disease: IV-6 had forced laughter, paranoid trends and faulty time relations. His sister IV-2 admitted a loss of memory coincident with other early signs, and she performed poorly in simple tests. V-2 and IV-9 were mentally deficient before the onset of ataxia, but further deterioration was not apparent during the disease; on the contrary, V-2 performed better in tests during ataxia than prior to it, in spite of a pellagra-like deficiency syndrome.

Londe [5] stated the opinion that mental enfeeblement was of some differential value in distinguishing Friedreich's disease from Marie's ataxia, claiming it was more frequent in the latter. Sjögren [16] demonstrated equal incidence of mental signs in the two forms of ataxia and remarked that they were often prominent in the late stages. Whyte [46] stated that when dementia was associated with Friedreich's disease it was earlier and severer than in the ataxia described by Londe. Dementia was part of the clinical picture in the members of the families reported by Neff,[28] Walter and Roese,[37] Schröder,[27] Curschmann [31] and Classen.[42] Classen and others noted dementia in siblings of ataxic persons. Bergman [34] observed failure of memory coincident with other early symptoms of ataxia. Knoepfel and Macken [47] performed mental tests on 15 patients with hereditary ataxia, and found emotional lability, irritability, loss of comprehension, poverty of association and general intellectual impairment.

GENERAL PHYSICAL FEATURES

Skeletal Deformities.—Skeletal deformities were noted in 6 members but were not confined to those with ataxia. IV-4 and V-11 had pes cavus with ataxia, but V-13 and V-23 also have this deformity, although they are under the age of onset. Others with and without ataxia had high arches (V-8, V-10, IV-21). It is of interest that outright pes cavus was confined to the women of this family. Scoliosis was present

46. Whyte, J. M.: Four Cases of Friedreich's Ataxia, with a Critical Digest of Recent Literature on the Subject, Brain **21**:72, 1898.

47. Knoepfel, H. K., and Macken, J.: Le syndrome psycho-organique dans les hérédo-ataxies, J. belge de neurol. et de psychiat. **47**:314, 1947.

in IV-26, and a slight curvature of the spine was noted in IV-32, IV-36 and V-7. Kyphosis was a striking feature in IV-6 and V-2.

Foot deformities, especially pes cavus, are common in Friederich's ataxia and sometimes appear as initial signs; scoliosis is occasionally associated but often appears independent of malformations of the feet. These two skeletal phenomena have been important in differentiating hereditary spinal (Friedreich's) ataxia from hereditary cerebellar ataxia, since they are uncommon in the latter. Deformities are widely reported in the literature dealing with dominant hereditary ataxia. In this review, scoliosis was present in the cases reported by Josephy [38] and Morris [25] and was a prominent feature in the members of the family reported by Classen.[42] Deformities of the feet were variously described as pes cavus, talipes equinus and pes planus.

Gastrointestinal System and General Nutrition.—The severe epigastric pain experienced by IV-16 and IV-28 was similar to that described in the cases of Klippel and Durante,[8] Josephy [38] and Ten Cate.[32] Roentgenologic studies with contrast mediums on IV-16 revealed no evidence of disease, and a test meal yielded a normal amount of free acid. Loss of weight usually accompanied the disease in this family, although IV-32 and IV-2 are notable exceptions. Loss of weight occurred early in III-7, IV-16, IV-21 and IV-30 and late in IV-6 and IV-43.

Genitourinary System.—Incontinence was said to have marked the end stages of the disease in III-1, and the urinary disorders were transmitted to the ataxic members in her progeny. IV-2 had urinary frequency, IV-4, bouts of urinary retention and cystitis in the advanced stages of the disease, and V-5, dribbling incontinence at 25 years of age. IV-32 has urgency, associated with frequency and nocturia. Incontinence was mentioned in some of the cases reported by Brüggendieck,[36] Brown [29] and Keiller.[44]

SUMMARY

Hereditary ataxia appeared as a dominant hereditary trait in 45 members of a family numbering 342. Four representative cases are reported to illustrate the clinical forms assumed by the disease.

1. *Hereditary Spinal Ataxia* (Friedreich's ataxia).—Ataxia in 1 member, possibly in 2, conformed to the diagnostic triad—onset prior to the age of 20, absence of deep reflexes and skeletal deformities—which distinguishes hereditary spinal ataxia.

2. *Hereditary Cerebellar Ataxia*:—Subgroup A (a syndrome resembling hereditary spinal ataxia) comprised 7 members who were closely related to the 2 members with the spinal form of hereditary ataxia. These members had normal or hypoactive reflexes and prominent coordinative disturbances; they also exhibited earlier and severer involve-

ments of deep sensibility, more optic nerve atrophy and nystagmus and minimal signs of involvement of the pyramidal tract.

Subgroup B comprised 12 members who had hyperactive reflexes and moderate coordinative disturbances. Whereas only 1 member of subgroup A exhibited disease of the pyramidal system, certain members of subgroup B had prominent pyramidal signs together with cerebellar dysfunction. Signs implicating the posterior columns and/or posterior roots appeared late, and optic nerve atrophy was uncommon.

3. *Hereditary Spastic Paraplegia.*—Two members, both second cousins of the 20 members making up the other groups, had a variant form of ataxia—hereditary spastic paraplegia. The initial signs appeared in the lower extremities and remained localized for several years. The degenerative process was limited essentially to the pyramidal system. Although 1 of these members still has no signs implicating the cerebellum or its pathways, the other has shown a slight intention tremor of the fingers in the late stages of the disease. Neither member had nystagmus, and 1 patient, who was observed five years after onset, was the sole member of the series without a speech disorder.

The material on which the discussion is based was obtained from examinations of 13 members by me and of 9 members by other physicians. The age of onset, known for 32 members, averaged 26.5 years, with a range of from 17 to 35 years. Using the existing data, it was possible to demonstrate the phenomenon of anticipation, for age at onset averaged 2 to 4 years earlier in each succeeding generation. The average duration of the disease was 10.2 years for 21 members, and the duration was slightly shorter for members in whom onset was at an early age. The average age at death for 27 deceased members with ataxia was 36.8, tending to be somewhat earlier for the women of the family. Pneumonia was the commonest immediate cause of death.

The disease in this family affected diverse structures within the central nervous system. However, the initial signs and those most frequently observed indicated particularly serious damage to the cerebellum and/or its pathways and to the facial, vagus and hypoglossal nerves. The disease did not remain localized, for the emergence of new neurologic signs throughout the course of the disease was evidence of its spread to other structures. Muscular and optic nerve atrophy, static tremors and a disturbance in deep sensibility were the signs which appeared particularly in the late stages and were clear indications of the extension of the disease process in the central nervous system. The chances of demonstrating a particular neurologic sign in members of this series depended on the type of syndrome which had evolved, the stage to which the ataxia had progressed and the characteristics of the syndrome in closely related members.

POSTOPERATIVE SWEATING PATTERNS IN THORACOLUMBAR SYMPATHECTOMY AND SPLANCHNICECTOMY

LOUIS T. PALUMBO, M.D.
HARRY H. SAMBERG, M.D.
JEROME C. HOHF, M.D.
AND
EDMUND T. BURKE, M.D.
DES MOINES, IOWA

SINCE the advent of thoracolumbar sympathectomy as a treatment for primary hypertensive vascular disease, various tests have been used postoperatively to determine the extent of the sympathetic resection. One of the tests commonly employed is the Minor starch-iodine test, which is based on the change in color occurring when a starch-iodine mixture becomes moist with the occurrence of sweating.

The actual mechanism of sweating is not well understood. Best and Taylor[1] stated that the stimulus for sweat secretion is a rise in blood temperature, which has a twofold effect: the stimulation of nerve centers in the brain and the stimulation of heat receptors in the skin, which reflexly cause the secretion. This contention has been supported by other investigators.[2] With these two concepts of the mechanism of sweating in mind, i. e., direct stimulation via the sympathetic nerve fibers from the heat centers in the brain and stimulation via a reflex arc from the heat receptors in the skin along sensory nerves to the central nervous system, the motor component being the sympathetic nerve fibers to the sweat glands, it is logical to assume that sweating will not take place from either form of stimulation if the sympathetic nerves to

From the Department of Surgery (Drs. Palumbo, Hohf and Burke), the Department of Physical Medicine (Dr. Samberg), Veterans Administration Hospital.

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1. Best, C. H., and Taylor, B. B.: Physiological Basis of Medical Practice, Philadelphia, Williams & Wilkins Company, 1939, p. 1007.

2. Cushing, H.: Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C Thomas, Publisher, 1932, p. 55. Kuno, Y.: The Physiology of Human Perspiration, London, J. & A. Churchill, Ltd., 1934, p. 205. Martin, C. J.: Thermal Adjustments of Man and Animals to External Conditions, Lancet **2**:561, 1930.

that we believe it lends support to their postulate. They found that after lumbar, thoracolumbar or total sympathectomy there was still decreased skin resistance over the twelfth thoracic to the third lumbar dermatome areas (lower part of the abdomen and anterior surfaces of thighs), as well as scattered areas on the face and trunk. In order to locate just where these residual pathways might lie, postoperative patients with total sympathectomies were given spinal anesthesia and the level was checked at which the sympathetic activity of the twelfth thoracic to the third lumbar dermatome was obliterated. This was found to be above the second lumbar dermatome and at or below the twelfth thoracic dermatome. Finally, the anterior nerve roots at these levels were sectioned, resulting in complete sympathetic denervation of the leg. The conclusion drawn from this is that the residual innervation, after thoracolumbar sympathectomy, to the area from the twelfth thoracic to the third lumbar dermatome is derived from the anterior spinal root of the first lumbar nerve, and partially from the twelfth thoracic and second lumbar nerves. They then postulated that residual sympathetic pathways arise in these nerve roots, but this assumption did not satisfy the question of the location of the ganglia and the pathways of the postganglionic neurons to these areas. By blocking and section of the genitofemoral, ilioinguinal and iliohypogastric nerves, but not by periarterial sympathectomy of the femoral nerve, they found that these areas could be denervated. Since tetraethyl ammonium chloride produces block of the autonomic nervous system only when a ganglion cell is present, denervation of these areas by use of this drug led to the conclusion that a residual ganglionated system was present. They further postulated that the anterior nerve roots might supply preganglionic fibers to ganglion cells about the aorta or an adjacent region, which cells, in turn, send postganglionic fibers to the lumbar plexus, but not to the periarterial sympathetic fibers, and that the sympathetic innervation of the anterior area of the thigh is via these nerves of the lumbar plexus.

Hyndman, Wolkin and Van Allen[8a] took exception to these conclusions because they were based on skin resistance patterns, which, in their opinion, were not as valid as sweating patterns. The fact that our sweating patterns are very similar to the skin resistance patterns of Ray and Console lends support to the latter's postulation.

This inferential proof that residual sympathetic pathways remain after thoracolumbar sympathectomy may account for the unpredictable results of thoracolumbar sympathectomy in patients with hypertensive vascular disease, in that patients with similar disease states have different

8a. Hyndman, O. R.; Wolkin, J., and Van Allen, M. W.: Cell Stations in the Upper Sympathetic Chain: Evidence That Functional Regeneration of Sympathetic Nerves in Man Occurs Only in Postganglionic Neurones, J. Neurosurg. 5:521, 1948.

degrees of relief after the procedure. These differences have always been explained on the basis of the variable pathology of the disease, or on regeneration or readjustment of the sympathetic nerves which are left intact, but the difference may be due to incomplete denervation by reason of anatomic variations in the sympathetic pathways.

PRESENT STUDY

Thoracolumbar Sympathectomy and Splanchnicectomy.—The surgical approach to the structures to be excised was accomplished by an aperiosteal removal of the eighth or ninth rib from the angle, posteriorly, to the costal cartilage, anteriorly. The parietal pleura was then stripped from the thoracic cage to permit visualization

Fig. 1.—*A*, complete absence of sweating from the fifth thoracic (spinal cord) dermatome (level of the nipples) to the first lumbar dermatome (pubis), except for areas of sweating ranging from pinpoint to confluent on the right side of the abdomen at the twelfth thoracic and first lumbar levels. It will also be noted that there is absence of sweating on the lateral sides of the chest above the fifth thoracic dermatome, anteriorly about both axillas, on the right arm anteriorly, on the anteromedial surface of the superior part of the right forearm and on the anteromedial half of the left arm and forearm and of both hands. *B*, complete absence of sweating over both lower extremities anteriorly except for heavy pinpoint sweating of the anterolateral surface of the lower two thirds of the right thigh.

of the thoracic portion of the sympathetic chain and the splanchnic nerves. The lung was retracted toward the mediastinum. The greater, lesser and least splanchnic nerves were dissected to their point of origin from the sympathetic chain, where they were divided, and they were likewise divided inferiorly as they entered the celiac ganglion below the diaphragm. These nerves were completely excised. The sympathetic chain in the thoracic region was divided usually at about the fifth thoracic level. In some instances the dissection was carried higher. In

order to divide the chain at this level, it was necessary to carry the dissection somewhat higher, and in elevating the chain from the thoracic wall it was possible to disrupt sympathetic fibers of the adjoining levels about the site of transection of the chain. This technical factor may account for the partial and temporary loss of sweating in the upper extremity, as noted in figure 1 *A*.

The thoracosympathetic chain was then freed of all its communications and excised from the fifth down through the twelfth thoracic level. The lumbar portion of the chain was removed from the first through the third lumbar ganglion, as shown in figures 1 and 2. In some cases only parts of the upper lumbar portion of the chain and ganglia were excised. The extent of denervation in the various cases was influenced by the age of the patient, his condition during operation, the degree of hypertension, the anatomic variations and the technical features encountered.

Fig. 2.—*A*, absence of sweating over the posterior surface of the right arm. The left upper extremity is not shown. Except for return of some sweating over the first lumbar dermatome and part of the second lumbar dermatome, (lower part of the back), there is absence of sweating on the buttocks and the back below the fourth thoracic dermatome on the right and, roughly, below the third thoracic dermatome on the left.

B, complete absence of sweating over both lower extremities posteriorly. The absence of sweating on the upper extremities of this patient is somewhat more extensive than is usually found and is, therefore, not representative of the usual pattern.

Removal of the lumbar portion of the chain and ganglia through this approach at times posed a difficult technical problem. In some instances the chain in the lumbar region was excised by enlarging the hiatus in the diaphragm. In some cases it was necessary to divide the diaphragm so as to provide adequate exposure of the retroperitoneal space in order that the chain might be visualized and removed. Occasionally, resection of the twelfth rib was necessary to expose

and permit the removal of the lumbar portion of the chain when the decision was made that a more extensive sympathectomy was indicated.

After completion of the operation the lung was reexpanded under direct vision by positive bag pressure, and any remaining air in the extrapleural and intrapleural spaces was removed by suction through a catheter. The wound in the chest wall was then closed in layers, with the use of silk sutures.

Technic of Sweating Test.—Minor in 1927 utilized a color reaction occurring in a mixture of iodine and starch when moisture is present. List and Peet[9] described this test in detail.

"The part of the body which is to be studied is uniformly painted with the following solution: iodine (chemically pure), 1.5 to 2.0 Gm. castor oil 10 cc. and absolute alcohol to make 100 cc.

Fig. 3.—*A,* return of sweating on the lateral sides of the chest and down to the sixth thoracic dermatome, and about the axillas and both upper extremities. On the abdomen, the twelfth thoracic and the first lumbar dermatomes show return of sweating, which is more pronounced on the left side, although operation was done on this side twenty-nine days after that on the right side.

B, complete return of sweating over the right thigh anteriorly, the sweating being heavy on the lateral half, and pinpoint on the medial half. The left thigh anteriorly shows heavy pinpoint sweating over the entire lateral half and the upper medial half. The lower medial half of the left thigh and the region below both knees still show complete absence of sweating.

"The skin must be completely dry and clean before applying. The solution is nonirritant and innocuous; . . . however, the eyelids and the external genitalia should be avoided. After the mixture has dried, the skin has a greasy, dark

9. List, C. F., and Peet, M. M.: Sweat Secretion in Man: I. Sweating Response in Normal Persons, Arch. Neurol. & Psychiat. **39**:1228 (June) 1938.

yellowish appearance. The painted parts are then dusted with a fine rice powder, which easily adheres to the skin. The starch should be slightly pressed into the pores of the skin with the help of a cotton powder puff, but all excess should be fanned away. The skin so prepared has a white or ivory hue. [Two large electric bakers are placed over the patient.] . . . The moisture of the first sweat secretion produces an iodine-starch reaction. At first the individual openings of the sweat glands appear as fine, bluish black dots resembling poppy seeds. With increasing perspiration [the dots coalesce], forming violet-black areas. At an advanced stage the excessive moisture drips down, and as it rinses off the mixture of iodine and starch, the pink color of the skin reappears. The patient can be easily cleansed by hot water and soap."

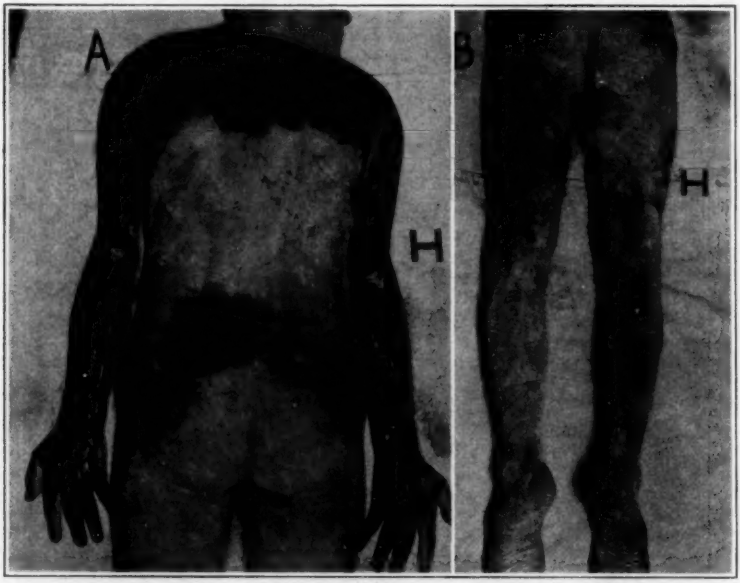

Fig. 4.—*A*, complete return of sweating over both upper extremities. On the back there is absence of sweating from about the fifth to the twelfth thoracic dermatome. On the lower part of the back, sweating has returned from the twelfth thoracic to the third lumbar dermatome, although it is not as pronounced as on the upper part of the back or the forearms.

B, complete absence of sweating over the buttocks and lower extremities posteriorly, except for return of a narrow strip of light sweating along the lateral margins of the upper two thirds of both thighs posteriorly.

Any areas of light sweating may be considered as areas of partial denervation,[4] as shown by studies of skin resistance.

We have found that adhesive tape, which is often applied to hold a dressing, interferes with the test, even though the adhesive substance may be thoroughly cleansed from the skin with ether. We feel, therefore, that several days should elapse, while daily cleansing of the skin with ether is carried out, before the test is performed.

To aid in the production of diaphoresis through central stimulation, the patient is given 15 grains (0.975 Gm.) of acetylsalicylic acid just before he reports for the test and 2 cups of hot tea just before the bakers are applied. The minimum heating period should be thirty to forty-five minutes, in order that sweating may be complete.

Results of Denervation As Evidenced by Sweating Patterns.—Since April 3, 1947, thoracolumbar sympathectomies have been performed on 11 patients for severe hypertensive vascular disease. The lumbar portion of the sympathectomy was not carried out to the same extent in each case, for reasons explained elsewhere in this paper. Eighteen postoperative sweating tests were made on 10 of these 11 patients. On only 7 of the 10 subjects were we able to secure follow-up sweating tests.

The accompanying photographs are representative of our findings when the lumbar portion of the sympathetic chain down to and including the third lumbar sympathetic ganglion was excised. In the particular patient shown the sympathetic chain and ganglia were excised from above the fifth thoracic sympathetic ganglion to below the third lumbar sympathetic ganglion, bilaterally. The first sweating test, on Jan. 1, 1948 (figs. 1 and 2), was performed forty-five and sixteen days after the thoracolumbar sympathectomies and splanchnicectomies, on the right and left sides, respectively.

The second sweating test (figs. 3 and 4), on June 3, 1948, was performed one hundred and forty-one days after the first sweating test.

COMMENT

The sweating patterns in this series of cases conform with the investigation of reports of others in this field. In evaluating the results for this series, as well as those reported in the literature by other groups, it is necessary to ascertain whether the surgical denervations carried out are identical in scope.

The areas of resumption of sweating of the skin from the twelfth thoracic to the third lumbar dermatome after a period of several weeks were fairly constant in all the various series reported. There are, no doubt, variations in other areas of the body which up to this time have not been thoroughly investigated. However, in the distribution of the thoracolumbar segment of the sympathetic nervous system the areas described reveal a persistent and similar pattern of return of sweating. It is assumed from these studies, and from the reports of Ray and Console [4] and Grimson,[6] that in these dermatome areas residual sympathetic pathways remain which most likely do not pass through the ganglionated sympathetic trunks of this area and, therefore, are not divided during this type of surgical procedure.

CONCLUSIONS

The problem of the return of sympathetic activity, as manifested by the return of sweating, after thoracolumbar and total sympathectomy is presented.

The question whether this return of activity is due to nerve regeneration, development of intrinsic sympathetic function, local response to humoral stimuli or incomplete denervation is discussed.

There is evidence to support the contention that the variation in postoperative results is due to incomplete denervation because of sympathetic pathways that do not traverse the sympathetic trunk.

Changes in sweating patterns correspond to changes in electrical skin resistance, as determined with the dermometer by various investigators.

There is evidence that these residual pathways are a ganglionated system. At present the location of this system is not known, although its postganglionic elements are thought to accompany some of the nerves of the lumbar plexus in the sympathetic innervation of the lower extremities.

THIOPENTAL U. S. P. (PENTOTHAL®) TREATMENT OF ALCOHOLISM

FREDERICK LEMERE, M.D.
AND
PAUL O'HOLLAREN, M.D.
SEATTLE

DURING the past fourteen years over 5,000 patients have been treated for chronic alcoholism at the Shadel Sanitarium, in Seattle. The cornerstone of this treatment has been the conditioned reflex method of producing an aversion to the sight, taste, smell and thought of alcoholic beverages by means of the drug emetine hydrochloride.[1] A follow-up study on 4,096 of these patients treated over a thirteen year period showed that 51 per cent had remained abstinent since treatment.[2]

Although these results were gratifying, we believe that they could be improved on by more adequate treatment of the underlying neurosis often present in alcoholic patients. With this idea in mind, we began using thiopental (pentothal®) sodium narcosynthesis as a short cut to psychotherapy of these patients.[3] The results have been so encouraging that we have used thiopental more and more as an adjunct to conditioning until at present 30 per cent of our patients are receiving the drug, as well as conditioning therapy.

TECHNIC

The first thiopental treatments are given as prolonged interviews with the patient under narcosis. Two grams of thiopental sodium is added to 200 cc. of sterile water and given intravenously by the drip method. In this way, the depth

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From the Shadel Sanitarium.

W. L. Voegtlin, W. R. Broz, W. Tupper, W. Berard and C. A. Shadel assisted in this study.

Read before the Section on Nervous and Mental Diseases at the Ninety-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 10, 1949.

1. Lemere, F.; Voegtlin, W. L.; Broz, W. R.; O'Hollaren, P., and Tupper, W.: Conditioned Reflex Treatment of Chronic Alcoholism: VII. Technic, Dis. Nerv. System **3**:1 (Aug.) 1942.

2. Lemere, F., and Voegtlin, W. L.: An Evaluation of the Aversion Treatment of Alcoholism, Quart. J. Stud. on Alcohol, to be published.

3. O'Hollaren, P.: Pentothal® Interview in the Treatment of Chronic Alcoholism, California Med. **67**:382 (Dec.) 1947.

of narcosis can easily be controlled over a long period, and the interviewer is left free to make notes and check a questionnaire covering salient points in the alcoholic history. Questioning is carried out with the patient at a level of narcosis deep enough to produce subsequent amnesia for the interview. The questionnaire is usually completed in two or three sessions, and in subsequent treatments the drug is given by the syringe method. These later interviews are much shorter and are used to check the patient's progress. They are terminated by strong suggestions against the use of alcohol and toward correction of faulty habits of thinking, after which the patient is put in a deep narcosis and allowed to sleep as long as possible.

A sleep of at least an hour, and preferably four to six hours, after administration of the drug is desirable. About 20 per cent of the patients sleep for less than one hour under thiopental, and in these cases amobarbital sodium (amytal sodium®) is substituted for the thiopental. The patient must not leave the sanatorium until he is mentally clear of the effects of the treatment; otherwise, he may take a drink while still under the effect of the barbiturate.

Thiopental can be given alone or in combination with conditioning. The combined treatment takes from ten to fourteen days and consists of from four to six conditioning treatments given on alternate days with from five to seven thiopental treatments. If given alone, one thiopental treatment is given each day for from five to seven days. After the initial course of treatments, the patient returns once a week for follow-up thiopental therapy. After several weeks, the interval between treatments is gradually extended to once every two to four weeks, the time depending on how nervous the patient becomes between treatments. Many patients who are working come in in the evening, receive their thiopental and sleep all night, leaving the next morning for work. Patients from a distance come in once a month for two or three thiopental treatments. If the patient has a desire to drink, a conditioning treatment is given in conjunction with the thiopental therapy at any time. Thiopental treatments are given for six months or longer, the period depending on the needs of the patient.

INDICATIONS

In general, thiopental therapy is indicated for patients who have trouble with nervous or emotional tension when sober and who drink to relieve this tension. More specifically, we have used thiopental alone or in combination with conditioning as follows:

1. Combined conditioning and thiopental therapy is given any patient who drinks primarily to relieve nervous or emotional tension.

2. Combined treatment is given any patient with a history of psychopathic personality, neurosis or psychosis or with a criminal record.

3. Combined treatment is given all patients under 30 years of age. Conditioning alone is of little value with the younger alcoholic patient. Presumably, alcoholism in a younger person means a severer personality deviation than in an older patient.

4. Thiopental is given alone or in combination with reconditioning to patients who have relapsed after one or two previous conditioning treatments.

5. Thiopental is given alone to a few patients who are unable to take the conditioning treatment because of some physical contraindication, such as a diseased heart.

Although we have been able to give thiopental to only 30 per cent of our patients, we believe that it would have helped about half our patients. The remaining half seem to be quite free of any undue nervous or emotional tension when not drinking and probably would not benefit from the drug.

COMPLICATIONS

A few patients do not tolerate intravenous use of barbiturates and become so wild and unmanageable under their influence that treatment has to be discontinued. A few patients periodically become so tense that they have to be kept under almost continuous thiopental narcosis for two to four days or they would surely drink unless so relieved. These extremely tense patients are difficult to treat, and special nurses and continuous administration of thiopental by the drip method or repeated intravenous injections of amobarbital are required.

One would think that patients might become dependent on thiopental, but in our experience this has been infrequent. We never give thiopental treatments oftener than once a week, and most patients can gradually be weaned away from treatments over a period of six months. Those few who seem to need thiopental over a longer period, such as a year or two, are still far better off than when drinking.

Four patients have consistently had an increase in temperature of 2 or 3 degrees (F.) after thiopental, and because of this their treatment had to be discontinued. Occasionally patients will cough or vomit under thiopental narcosis, and they must be watched closely to avoid aspiration or asphyxia. It is best to have the patient skip the meal before treatment and to have a nurse in constant attendance because of this possible complication. One patient had reacted to thiopental with such a severe angioneurotic edema that further treatment had to be discontinued.

RESULTS

During the three year period from Jan. 1, 1946 to Jan. 1, 1949 we treated 503 patients with thiopental sodium alone or combined with conditioning. The results of treatment as of March 1, 1949 were unknown for 24 patients. An accurate follow-up history of the remaining 479 showed that 57 per cent had been abstinent since initiation of their treatment (chart 1).

A breakdown of these results shows that 219 patients were given the combined thiopental and conditioning treatment on their first admission, with an abstinence rate of 68 per cent (chart 2); 23 patients

were given thiopental alone without conditioning on their first admission with an abstinence rate of 44 per cent (chart 3); 166 patients were retreated with combined reconditioning and thiopental after they had relapsed on conditioning alone, with an abstinence rate of 49 per cent (chart 4); 71 patients were retreated with thiopental alone after having

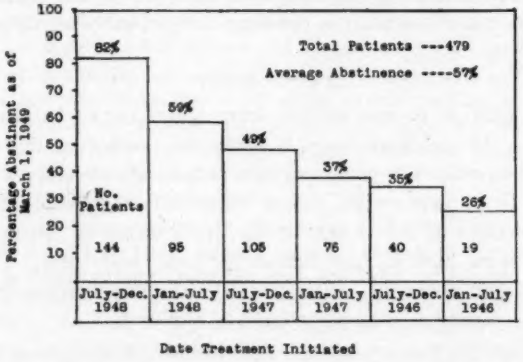

Chart 1.—Total results with thiopental alone and combined with conditioning.

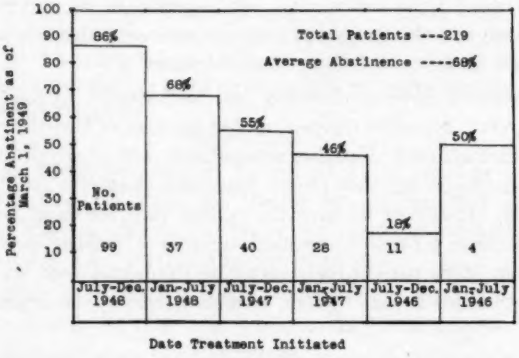

Chart 2.—Results of combined conditioning and thiopental therapy given on first admission.

relapsed on conditioning, with an abstinence rate of 45 per cent (chart 5).

We wish to stress the fact that these patients treated with thiopental represent our most difficult cases and that the prognosis in this group of patients was usually hopeless before the advent of this drug.

In an effort to determine how much of the value of thiopental is due to the associated psychotherapy and how much to its pharmacologic

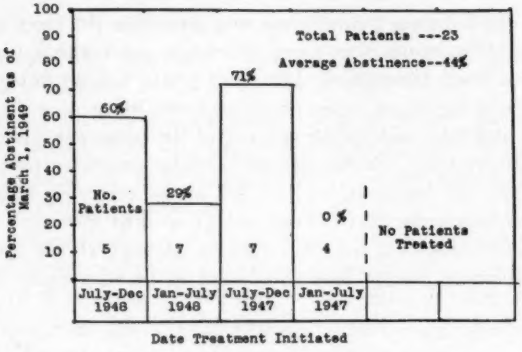

Chart 3.—Results of thiopental alone on first admission.

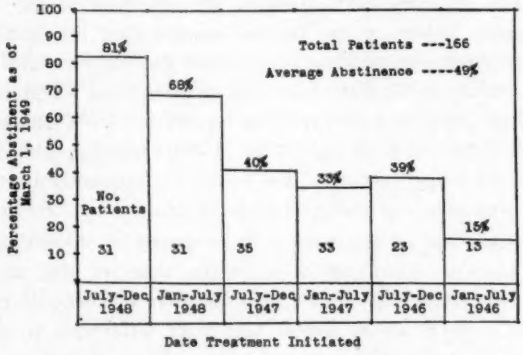

Chart 4.—Results of combined reconditioning and thiopental after relapse on conditioning therapy alone.

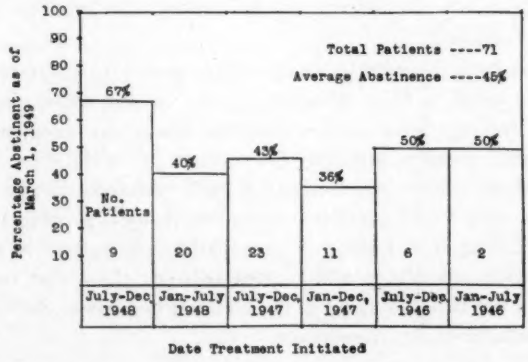

Chart 5.—Results of thiopental after relapse on conditioning alone.

action, we divided these patients into two groups on the basis of alternate admissions. One group was given extensive psychotherapy, averaging about twelve hours per patient. The other group was given brief psychotherapy, averaging about three hours and consisting of a discussion of immediate problems and strong support of the patient in his determination to stop drinking. Of the group receiving extensive psychotherapy and thiopental 58 per cent, and of the group receiving brief psychotherapy and thiopental 56 per cent, have remained abstinent. We have been unable to evaluate the effectiveness of suggestions given under thiopental narcosis except that they seem to be of definite help.

COMMENT

The finding that brief psychotherapy with thiopental is as effective as extensive psychotherapy with the drug suggests that the pharmacologic action of thiopental sodium is as important as the associated psychotherapy. Indeed, it has become evident that thiopental sodium, of itself, has a remarkable ability to relieve the nervous and emotional tensions of the alcoholic patient. Such statements as "This is the first time in twenty years that I haven't felt worried," or "Pentothal® clears my mind so I can think straight," or "I don't need a drink any more because I'm no longer nervous" are heard so frequently from patients taking the drug that one cannot but be impressed by its effectiveness.

The physical and mental relaxation produced by thiopental is much more dramatic in the alcoholic neuroses than in the nonalcoholic neuroses. This is probably due to the peculiar biochemical makeup of the alcoholic patient, which makes him react differently to thiopental, as well as to alcohol. In fact, thiopental might be looked on as a substitute for alcohol—a substitute that gives the same relief from tension as that afforded by alcohol, but one that can be controlled by the physician and gradually withdrawn as the patient develops the ability to live without alcohol.

Thiopental is superior to orally administered barbiturates in that there seems to be a basic difference in its action when given intravenously. Another advantage is that the dosage can be controlled by the physician, thereby avoiding the danger of barbiturate addiction which so often follows self medication with sedatives by the alcoholic addict. We have found a tablet [4] containing 8 mg. (⅛ grain) of belladonna and 32 mg. (½ grain) of phenobarbital fairly safe in those few cases in which sedation is still needed between thiopental treatments. Patients will not take too many of these tablets because of the unpleasant effect of belladonna on overdosage.

4. Belap® 2, Haack Laboratories, Inc., Portland, Ore.

SUMMARY AND CONCLUSIONS

1. Thiopental (pentothal®) sodium is a valuable addition to the treatment of alcoholism.

2. Thiopental has a remarkable ability to relieve the nervous and emotional tension that so often causes the alcoholic person to drink.

3. Thiopental is best combined with conditioned reflex aversion treatments and psychotherapy.

4. A follow-up study on 479 unusually difficult patients treated with thiopental alone or combined with conditioning and psychotherapy over a period of three years showed that 57 per cent still were abstinent.

5. Thiopental has a pharmacologic effect in alcoholism over and above the benefits of the associated psychotherapy.

6. The physical and mental relaxation produced by thiopental is much more dramatic in the alcoholic neuroses than in nonalcoholic neuroses.

7. Thiopental therapy is in part a substitutive therapy. It gives much the same relief from tension as that afforded by alcohol, without the harmful effects of the latter. Its use can be controlled by the physician and gradually withdrawn as the patient learns to live without alcohol.

EFFECT OF "MALONONITRILE" ON PHYSICAL AND MENTAL STATUS OF SCHIZOPHRENIC PATIENTS

DIXON MEYERS, M.D.
THOMAS E. SHOEMAKER, M.D.
WILLIAM C. ADAMSON, M.D.
AND
LOUIS SUSSMAN, M.D.
PHILADELPHIA

IN 1948 Hydén and Hartelius,[1] of the Caroline Institute, Stockholm, published a monograph covering the extensive work they had done on the effect of the drug "malononitrile" in increasing the protein metabolism and cellular function of the ganglion cells of the central nervous system. They were able to demonstrate by the microspectrographic technic of Caspersson [2] that the brain tissue taken at frontal lobotomy in 11 schizophrenic patients and in 1 patient with an endogenous depression differed from the tissue taken post mortem on 4 reputedly "normal" persons who had died suddenly not more than three to five hours before the specimen was taken.

The threefold differences which they described between the material from the psychotic patients and that taken from normal brains consisted in the observations that in the large pyramidal cells of the third layer of the frontal cortex (1) the nucleolar and nuclear apparatus were poorly developed in the brains of the psychotic patients and "normally" developed in the brain tissue of nonpsychotic patients, (2) the protein content of the cells from the brains of the psychotic patients was lower than that of the cells of "normal" brain tissue and (3) the ribonucleic acid content was so low in the material from the psychotic patients as to be scarcely detectable and relatively large in normal brain tissue.

This investigation was supported by the Hall-Mercer Hospital.

"Malononitrile" was made available through the courtesy of Smith, Kline & French, Laboratories, Philadelphia.

1. Hydén, H., and Hartelius, H.: Stimulation of the Nucleoproteinproduction in the Nerve Cells by Malononitrile and Its Effect on Psychic Functions in Mental Disorders, Acta psychiat. et neurol., 1948, supp. 48, p. 1.

2. Caspersson, T.: Methods for the Determination of the Absorption Spectra of Cells Structures, J. Roy. Micr. Soc. **60**:8, 1940.

Using the drug "malononitrile" ($CN\text{-}CH_2\text{-}CN$), Hydén and Hartelius found that by an intravenous injection of 3 to 4 mg. per kilogram of body weight, they could increase the nucleoprotein content of the pyramidal cells of 56 rabbits and could double the ribonucleic acid content of these cells without any toxic effects to the animals. They also observed that lethal doses of "malononitrile" could be given with the specific detoxifying agent sodium thiosulfate ($Na_2S_2O_3$), over an extended period with no demonstrable effects on the rabbits. (This relation between "malononitrile" and sodium thiosulfate was first demonstrated in 1896 by Heymans and Masoin.[3])

CLINICAL DEVELOPMENT

With this work as a background, Hydén and Hartelius attempted to determine the effect of 4 to 6 mg. of "malononitrile" per kilogram of body weight in 66 patients with schizophrenia or endogenous depressive psychoses. The conclusions were as follows:

> In cases of endogenous depression, malononitrile causes an initial accentuation of psycho-motor retardation and depression, followed by psycho-motor spontaneity and euphoria.
>
> In schizophrenia, malononitrile causes an initial accentuation of autism and katatonia, followed by increased contact and mental release.
>
> In two cases malononitrile provoked typical epileptic attacks, although there had been no epilepsy in the history of these patients.

They expressed the opinion that the effect of "malononitrile" on the psychic function is "in the nature of a stimulation" and that there appears to be a correlation between the psychic function and the nucleoprotein metabolism of the nerve cells."

In 1948, at the annual meeting of the American Psychiatric Association, MacKinnon, Hoch, Cammer and Waelsch,[4] of the New York State Psychiatric Institute, reported their findings on the use of "malononitrile" in 9 schizophrenic patients. Using doses varying from 2 to 4 mg. per kilogram of body weight and allowing fifteen to twenty minutes for the drug to act before giving the antidote, sodium thiosulfate, they detected "no benefit as a result of the treatment." In addition, they stated that "with the exception of mild toxic reactions after injections, the patients displayed no improvement of their psychotic conditions. Also, that no alterations in their emotional reactions were observed." It was the opinion of these investigators that "malononitrile" had no clinical application.

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3. Heymans, J., and Masoin, P.: Action antitoxique l'hyposulfite de soude vis-à-vis des dinitriles normaux, Arch. Pharmacod. **3**:77, 1896.

4. MacKinnon, I.; Hoch, P.; Cammer, L., and Waelsch, H.: The Use of Malononitrile in the Treatment of Mental Illnesses, Am. J. Psychiat. **105**:686, 1949.

PRESENT INVESTIGATION

Selection of Cases.—When it was determined to try "malononitrile" in the treatment of patients at the Pennsylvania Hospital, we decided first to use the drug in cases of schizophrenia in which other forms of drastic therapy had been tried without improvement. The patients selected were from the younger age group and had no evidence of organic disease. Three of these patients had had both insulin and electric shock therapy in the past, 2 had had prolonged courses of electric shock therapy alone, and 1 had received no drastic therapy during his five years of hospitalization. The total duration of hospitalization varied from seven to three years.

Method.—Patients were treated in a separate unit, where they were taken on the treatment mornings. Treatment was given at about 8:30 a. m. with the patient in a fasting state. The patient was returned to his room after treatment, where he was given breakfast. A typical treatment was somewhat as follows: The patient was brought to the unit, where he was put to bed. The blood pressure, pulse and respiration were checked and the readings recorded. The patient was then given an intravenous injection of 5 per cent "malononitrile" in distilled water. The nurse then checked the pulse and respiration about every five minutes and recorded any verbalization and any physical change the patient might show. Usually there was very little change in the blood pressure during the treatment. In a few instances there were a slight rise in the systolic pressure and slight widening of the pulse pressure. Usually about five minutes after the injection there was flushing of the face, which became progressively more pronounced throughout the treatment. The patient complained of feeling hot, of dryness of the mouth and occasionally of pounding in the head. After about ten to fifteen minutes the pulse rate began to increase, rising gradually to as high as 120 to 140 a minute in the various patients. After twenty to twenty-five minutes the patient began to complain of nausea. He became increasingly restless, frequently rolling about in bed; the veins of the head and neck became greatly distended, the extremities were cold and the patient was obviously in acute distress. Vomiting occurred in about thirty minutes in most cases. Treatment was terminated by intravenous injection of a 5 per cent solution of sodium thiosulfate. Recovery was dramatic. In two to three minutes the tachycardia was relieved, the retching stopped and the flushing disappeared, and within three to five minutes the patient was completely at ease. One patient stated that the sensation during the action of the "malononitrile" was "the most awful thing I have ever felt" but that the feeling of well-being which he experienced after treatment was "worth it." In some patients this feeling passed before the next treatment; in some it became progressively more pronounced throughout the course of therapy. The patients showed no ill effects after treatment and, on return to their rooms, ate a hearty breakfast. On two occasions vomiting occurred after the patient's return to the room. On both occasions the injection of sodium thiosulfate was repeated, and no further difficulty was encountered.

The doses varied from 3 to 6 mg. per kilogram of body weight. The time of treatment varied from about twenty-one to sixty minutes, with the average about thirty minutes. The amount of the drug given seemed to have little effect on the length of treatment; that is, we observed patients who received relatively large doses and remained under the effect of the drug over thirty minutes before vomiting occurred, and we saw patients with smaller doses vomit in twenty-five minutes. This period also varied for the individual patient. We are at a loss to explain the variations from the original work with regard to the length of time that treatment

required. The original investigators waited one hour before terminating the treatment and were not apparently troubled by patients vomiting. The volume of the thiosulfate solution was always slightly more than three times that of the "malononitrile" solution.

To 3 patients we gave intravenous infusions of a protein hydrolysate ("parenamine," [5] which is a preparation of amino acids in 6 per cent dextrose), on the theory that if there was an additional demand for protein materials they should be supplied. Our series is not large enough to permit us to draw any conclusions as to the efficacy of this form of therapy.

On 3 patients electroencephalograms were taken during the treatments. Among the other patients there was not enough cooperation to allow a readable record to be taken. Definite and marked changes of a similar nature were found in all 3 cases. For the sake of brevity, a composite picture will be presented, rather than the individual records.

The pretreatment record showed a low amplitude, 10 per second rhythm with an occasional 3 to 4 per second rhythm appearing. Immediately after the injection of "malononitrile" there was an increase of the amplitude in the 10 per second waves. In two to five minutes bursts of slower (3 to 4 per second) waves began to appear. As the record progressed, the amplitude of the slow waves increased and that of the faster waves decreased. After about five minutes the 10 per second waves had almost completely disappeared; there was predominance of 3 to 4 per second waves, with some slower waves appearing. In the later part of the record there were so many artefacts due to motor restlessness that an accurate interpretation was impossible. After the injection of thiosulfate there was, within one-half minute, a reappearance of the 10 per second waves. The amplitude of the slow waves decreased, and these tended to disappear. In about three to five minutes the pretreatment rhythm was reestablished.

Specimens for determination of the blood sugar were taken before, during and after termination of the action of the drug. We were unable to demonstrate any consistent pattern of changes in these specimens. The changes which were present were small and extremely variable, even for the same patient.

CLINICAL RESULTS

The first 5 patients to receive this treatment were white men between the ages of 19 and 24 years. Their terms of hospitalization varied from three to seven years. One of these patients had received no drastic therapy during his five years in the hospital; 1 had received a course of thirty insulin comas; another, fifty-eight insulin comas and metrazol® therapy, and 2, both insulin and electricshock therapy.

All these patients undoubtedly had schizophrenia. The number of treatments with "malononitrile" varied from fourteen to thirty-three.

One patient failed to show any improvement, and treatment was stopped after the fourteenth session. Two of the patients showed improvement during the course of treatments but relapsed to the pretreat-

5. Parenamine (3 per cent in 6 per cent dextrose) was made available through the courtesy of the Department of Medical Research, Winthrop-Stearns, Inc,. New York.

ment level before the termination of the therapy. This improvement was measured in terms of apparent decrease in tension and increased interest in their environment, personal appearance and personal hygiene. It must be pointed out that both these patients had had previous periods of spontaneous improvement, similar to that observed at this time. Therefore, we hesitate to attribute this improvement entirely to the effects of the treatment.

Two other patients showed a more decided improvement, as measured in terms of increased contact with the environment, increased sociability, increased interest in personal appearance and increased ability to verbalize their feelings, as well as decrease in the previously mentioned symptoms of anxiety and tension. One of these patients had what appeared to be a relapse immediately after the end of treatment but then began to manifest progressively greater improvement, which continues to the time of this report. The other patient maintained his improvement for about one month after the end of treatment, when he relapsed to his pretreatment state.

In the case of the sixth patient there was controversy about the diagnosis. Several of the staff members felt that she was schizophrenic, while other preferred the diagnosis of psychopathic personality with pathologic emotionality. Certainly, she did not present a typical picture of schizophrenia, but, because she exhibited severe anxiety and tension and because of our observation that such symptoms seemed to be relieved by the drug, we decided to give her a course of treatments. She had had two periods of hospitalization during the four years prior to her transfer here from a psychiatric hospital in New England.

On admission to this hospital, the patient was tense and overactive. She was voluble and had rapid swings from tearful depression to superficial gaiety. There were periods of "panic" in which she was questionably delusional and had intense fears of impending disaster. She received a series of ten electric shock treatments, without much change. Treatment with "malononitrile" was started on Aug. 10, 1948. During the first seven treatments the patient showed no apparent change. After the eighth treatment, she said that she felt much better and showed more interest in hospital activities. During the following treatments she subjectively was less tense and objectively showed gradual improvement. During the seventeenth treatment she expressed the desire to go home and take care of her family. The patient received a total of seventeen treatments. The last 9 of these were accompanied with infusion of "parenamine." She continued to improve gradually and left the hospital about two weeks after the end of the treatment. We have just heard that she had a relapse and was admitted to another hospital four months after her discharge.

COMMENT

In view of the results reported, we feel that "malononitrile" does have an effect on the mental and physical status of psychiatric patients. The most prominent features which we observed were the relief of the physical and subjective symptoms of tension and the patients' increased ability to verbalize their repressed emotions. It should be emphasized that in these treatments every effort was made to minimize the psychotherapeutic factor, or the factor of suggestion. The patients went through exactly the same routine as before treatment, except for the time actually spent in the treatment situation. Every effort was made to avoid a discussion of personality problems during treatment, and, except for questions designed to elicit information about the immediate condition during treatment, there was no conversation between the physician giving the treatment and the patient. Most of the statements relative to improvement were made on the basis of observations by the nurses, because we wished to avoid the therapeutic effect of even relatively infrequent visits by a physician. Before treatment, the patient was merely told that he was to receive a "series of treatments," and, other than a purposely vague statement that it "might make him well," nothing was said of the action or possible effects. It is possible that if psychotherapy had been introduced during the periods of improvement, which 2 of the patients showed, a relapse could have been avoided. It is well known that results with insulin therapy and electric shock therapy are much better if intensive psychotherapy is combined with the treatments.

Our observations tend to support the findings of Hydén and Hartelius that "malononitrile" produces a change in psychiatric symptoms, although our results were not as encouraging as those they reported. One explanation of this might be that our patients were much more severely ill than theirs. Many of their patients had received no other form of therapy previously, and a great number had relatively mild depressions. There were also many with involutional psychoses in their series of 66 patients.

We feel that our results were better than those reported by MacKinnon and his co-workers, from New York. This may perhaps be explained by the fact that they used smaller doses and stopped the action of the drug much sooner than we did. What they describe as "toxic manifestations" we consider the normal action of the drug.

SUMMARY

Of the 6 patients treated with "malononitrile" by the method of Hydén and Hartelius, none recovered as a result of the treatment. All 6 showed pronounced physiologic and emotional reactions after injection of the drug. One showed no clinical improvement; 2, slight, transient

improvement, and 2, more decided and prolonged improvement. One patient, for whom there was some question of the diagnosis of schizophrenia, showed a decrease in the subjective and the objective evidence of tension and was able to leave the hospital. The question of the part which environmental factors played in her case cannot be answered.

Changes were demonstrated in the electroencephalograms of the 3 patients for whom records could be taken.

The blood sugar level apparently was not related to "malononitrile" therapy.

We feel that the results here outlined warrant further investigation. Patients to whom psychotherapy could be given at the same time as the drug and patients with illnesses of shorter duration should certainly be treated by this method.

EFFECT OF ELECTRICALLY INDUCED CONVULSIONS ON CUTANEOUS LYMPHATIC FLOW

M. D. ALTSCHULE, M.D.
AND
L. H. ALTSCHULE, M.D.
BOSTON

EARLIER work afforded data which indicated that accelerated flow occurred in cutaneous lymphatics when the amount of tissue fluid increased during the intravenous administration of solutions of electrolytes.[1] In view of the fact that fluid is lost from the circulation to the tissues during electrically induced convulsions,[2] it was considered of interest to study the behavior of the lymphatics of the skin before and after such seizures.

MATERIAL AND METHODS

Ten patients, ranging in age from 18 to 64, were studied; 8 were women. All were psychotic, but the type and severity of the mental disease varied. None had evidence of impairment of cardiac, renal or thyroid function. The method used was that previously described[1] and consisted in measurements over a period of fifteen minutes of the areas of wheals made by injecting a 1 per cent solution of Evans blue (T 1824). One wheal was made approximately fifteen minutes before the seizure was induced; increases in its area before the convulsion were compared with changes in area after it. A second wheal was made immediately before induction of the seizure and was observed for fifteen minutes after the end of the convulsion. In 9 instances the wheals were made on the flexor surface of the forearm; in the remaining 1 case they were placed over the medial aspect of the shin.

OBSERVATIONS

The areas of the wheals made approximately fifteen minutes before the convulsion increased by 0 to 28 per cent in the period up to the induction of the seizure; the average increase was 8 per cent. The increase

From the Laboratory of Clinical Physiology, McLean Hospital, Waverley, Mass., and the Department of Medicine, Harvard Medical School.

1. Altschule, M. D.; Freedberg, A. S., and McManus, M. J.: The Effects on the Cardiovascular System of Fluids Administered Intravenously in Man: V. Function of Cutaneous Capillaries and Lymphatic Vessels, Arch. Int. Med. **80**:491 (Oct.) 1947.

2. Altschule, M. D.; Cram, J. E., and Tillotson, K. J.: Hemoconcentration After Electrically Induced Convulsions in Man, Arch. Neurol. & Psychiat. **59**:29 (Jan.) 1948. Altschule, M. D., and Cline, J. E.: Decrease in Plasma Volume During Electrically Induced Convulsions in Man, Proc. Soc. Exper. Biol. & Med. **69**:598, 1948.

in area of the same wheals during fifteen minutes after the seizure was 0 to 19 per cent, with an average of 5 per cent. The wheals induced immediately before induction of the seizures showed increases in the area of 0 to 25 per cent in the fifteen minutes which followed the convulsions; the average was 4 per cent.

COMMENT

The fluid lost from the circulation during an electrically induced convulsion averages 15 per cent of the plasma volume, i. e., between 200 and 1,100 cc.[2] This fluid returns to the circulation in fifteen

Percentage Increase in Area of Wheal in Fifteen Minutes

Case No.	Before Convulsion	After Convulsion
1		
a	28	0
b	..	10
2		
a	0	0
b	..	0
3	..	0
4		
a	25	16
b	..	25
5		
a	0	0
b	..	0
6		
a	14	0
b	..	8
7		
a	0	13
b	..	0
8		
a	5	0
b	..	0
9		
a	0	19
b	..	0
10		
a	0	0
b	..	0
Average	8	4.5

to thirty minutes after the end of the convulsion.[2] The increased transudation is the consequence partly of increased filtering pressures,[3] although anoxia and metabolic changes in the muscles as factors cannot be ruled out. It is probable that most of the increased transudation occurs in the skin and underlying tissues; during the seizure intramus-

3. Silfverskiöld, B. P., and Åmark, C.: Disturbance of Circulation in Convulsions of the Epileptic Type: II. Arterial and Venous Pressure During Electroshock, Acta. med. Scandinav. **113**:191, 1943. Altschule, M. D.; Sulzbach, W. M., and Tillotson, K. J.: Effect of Electrically Induced Convulsions on Peripheral Venous Pressure in Man, Arch. Neurol. & Psychiat. **58**:193 (Aug.) 1947. Altschule, M. D., and Tillotson, K. J.: Modification by Curare of Circulatory Changes Occurring During Electrically Induced Convulsions in Man, ibid. **59**:469 (April) 1948.

cular tensions must be very high, and the elevated venous pressures which exist in the thoracic and abdominal vessels are counteracted by high intrathoracic and intra-abdominal pressures, which are present simultaneously.

The return of excessive quantities of fluid which enter the subcutaneous tissues could occur by way of capillaries or lymphatics or both. In a previous study it was shown that the lymphatics participate in the reabsorption of fluid lost from the circulation during the course of intravenous infusions in man.[1] In the present study on electrically induced seizures, however, no evidence of increased lymphatic function was found during the period of reabsorption of the fluid which had left the vascular bed. Since the levels of the venous pressure which exist during the period of reabsorption of excess tissue fluid after electrically induced seizures are similar to those which were found during the period of absorption of excess tissue fluid during intravenous infusions, it is apparent that other factors must be important. It is probable that the difference lies in the opposing changes in plasma protein concentration which occur during infusions of intravenous fluids, on the one hand, and convulsive seizures, on the other. In the former hemodilution occurs,[4] while in the latter hemoconcentration always develops.[2a] Reabsorption of tissue fluid into capillaries is retarded by hemodilution and favored by hemoconcentration. Fluid lost to the tissues after intravenous injection of solutions of electrolytes therefore returns to the vascular bed largely via lymphatics, while after electrically induced convulsions, as in the present study, such fluid is quickly reabsorbed into the capillaries as soon as venous pressures fall from the high levels which obtain during the seizure; increased lymphatic activity is not necessary.

CONCLUSIONS

No evidence of increased cutaneous lymphatic activity occurs during the period of reabsorption of fluid lost from the circulation during electrically induced convulsions. It is concluded that the hemoconcentration which occurs after seizures favors reabsorption of such fluid via the capillaries.

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4. Gilligan, D. R.; Altschule, M. D., and Volk, M. C.: The Effects on the Cardiovascular System of Fluids Administered Intravenously in Man: I. Studies of the Amount and Duration of Changes in Blood Volume, J. Clin. Investigation **17**:7, 1938.

OSTEOBLASTIC MENINGIOMA IN A CHILD

LEO MADOW, M.D.
AND
R. A. FARMER, M.D.
PHILADELPHIA

OSTEOBLASTIC meningioma is extremely uncommon in childhood. This is understandable, as meningiomas in general are rare in children and the osteoblastic type is an infrequent variety. Keegan [1] reported a meningioma in an 8 year old child. The 2 youngest patients in Cushing's series [2] dated their symptoms from approximately three years of age, and there were only 6 preadolescents in his entire group. In his cases of osteoblastic meningioma the earliest symptoms began at 30 years of age.

The exact number of osteoblastic meningiomas reported in the literature cannot be tabulated because of the failure of authors to enumerate the number of cases of this tumor found in their reported series and because of the variation in classifications used. Cushing, in addition to reporting 6 cases of his own, described 5 recorded by other authors. Bailey [3] reported 1 in his series of 27 meningiomas. Courville and Abbott [4] stated that they found bone formation in the fibrous type of meningioma. Globus,[5] in a study of 103 meningiomas, described bone formation in some of the tumors which he classified as meningioma omniforme. Bailey and Bucy [6] described 1 case of osteoblastic meningioma but did not say how many they had in their series. Gray [7] reported 1 in a series of tumors of the spinal cord. Freiman and

From the Department of Neurology, Jefferson Medical College of Philadelphia.

1. Keegan, J. J.: Meningioma in Child, Arch. Neurol. & Psychiat. **44**:439 (Aug.) 1940.

2. Cushing, H., and Eisenhardt, L.: Meningiomas, Springfield, Ill., Charles C Thomas, Publisher, 1938.

3. Bailey, O. T.: Histological Sequences in the Meningioma, with a Consideration of the Nature of Hyperostosis Cranii, Arch. Path. **30**:43 (July) 1940.

4. Courville, C. B., and Abbott, K. H.: Classification of Meningiomas, Bull. Los Angeles Neurol. Soc. **6**:21, 1941.

5. Globus, J.: Meningiomas, Arch. Neurol. & Psychiat. **38**:667 (Oct.) 1937.

6. Bailey, P., and Bucy, P. C.: Origin and Nature of Meningeal Tumors, Am. J. Cancer **15**:15, 1931.

7. Gray, E. D.: Calcification and Ossification of Spinal Tumors, Brit. J. Radiol. **15**:365, 1942.

Ficarra [8] found both bone and cartilage in a meningioma overlying the left cerebellar hemisphere. Certainly, less than 25 cases of osteoblastic meningioma have been reported in the literature.

The present case is presented because of the extreme rarity of the tumor in children and because it arouses interesting speculations concerning bone formation within meningiomas.

REPORT OF A CASE

Twelve year old girl with a history of jacksonian epilepsy for eight years. Upward deviation of the right eye, loss of upward and inward movements of the left eye and bilateral impairment of convergence. Almost complete deafness bilaterally. Paresis and underdevelopment of the right upper and lower extremities, with Babinski, Gonda and Chaddock signs on the right side. Huge calcified mass visible in roentgenograms. Successful removal of an osteoblastic meningioma.

History.—L. S., a 12 year old white girl, was admitted to the neurologic service of Jefferson Hospital on March 3, 1947, with a complaint of convulsions for the past eight years.

The parents stated that she was the fourth of seven children. Her birth history was normal. She walked at 8 months and talked at 10 months of age, and was considered to be mentally and physically normal until March 13, 1939, at the age 4 years 4 months, when she had an attack of rhythmic clenching movements of the right hand with flexion movements of the right forearm. This attack lasted about one minute and was not accompanied with other convulsive phenomena. Several weeks later a second attack occurred in the same fashion with the additional involvement of the right leg. During the ensuing year the seizures occurred once daily for two or three days every one to two weeks and lasted one to two minutes. The right upper and lower extremities and the right side of the abdomen were involved. There was no tongue biting, incontinence, unconsciousness or postictal stupor.

During 1940, the year following development of her symptoms, the right side of the face began to twitch during the seizures. About March 1945, six years after onset, she experienced an aura of pulsations in the chest; from then on the attacks were associated with unconsciousness and tongue biting. She had no incontinence with any seizure. In December 1946, four months before admission, she had an unusually hard seizure during sleep. Whereas her hearing had been clinically normal, she was unable to hear normally after recovery from this seizure. This faculty steadily decreased, so that she was almost totally deaf by the time of admission. There was no history of disease of the paranasal sinuses or middle ears, or of tinnitus or vertigo.

Several months prior to admission she began to notice "pins and needles" sensations over the right side of her body.

For four years she had had partial paralysis of the extraocular muscles of both eyes. For one year she had had mild frontal headaches. The past history was otherwise normal except for an episode of measles during infancy. The family history contained no pertinent facts.

Examination.—Physical examination revealed a pleasant, cooperative girl of normal size whose abnormalities were confined to the neuromuscular system. She

8. Freiman, I. S., and Ficarra, B. J.: Osteochondroblastic Meningioma of the Left Cerebellar Hemisphere, Arch. Path. **35**:900 (June) 1943.

appeared to be mentally retarded. The pupils were equal and regular and reacted well to light, in accommodation and to consensual stimuli. There was ptosis of the left eyelid covering one third of the palpebral fissure. Extraocular movements were normal except for loss of inward and upward movements of the left eye, a tendency toward upward deviation of the right eye and impairment of convergence bilaterally. The corneal reflexes were normal. There was papilledema of 3 D. bilaterally, with no hemorrhages or exudates. The visual fields could not be accurately tested but were normal with the confrontation test. The masseter and temporal muscles contracted well. Pain sensation was inconstantly impaired over the left side of the face. There was weakness of retraction of the right corner of the mouth with both voluntary and emotional stimulation. She was barely able to hear loud conversational tones. Bone conduction was feebly appreciated bilaterally; air conduction was absent. Her voice was moderately harsh but not entirely without modulation. There was no weakness of the palate. The trapezius and sternocleidomastoid muscles were equally strong on the two sides. The tongue protruded in the midline.

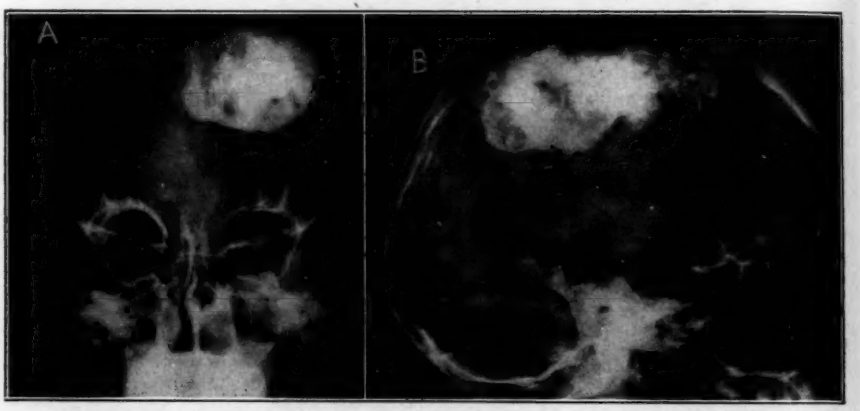

Fig. 1.—Anteroposterior and lateral roentgenograms of the skull, showing the calcified mass.

Finger to nose and heel to knee tests were impaired on account of weakness on the right side. There was no dyssynergia. The gait was steady, but the right leg was circumducted and spastic in walking. The Romberg test was normal.

The upper and lower limbs on the right side were one-third smaller than those on the left, which were normal. The limbs on the right side were weak, particularly the leg. All deep reflexes were active, those on the right side being faster. The abdominal reflexes were active and equal on the two sides. Babinski, Chaddock and Gonda signs were elicited on the right side.

Pain, position and vibration senses were normal except for inconstant hypalgesia over the left side of the face and trunk and over the left arm.

Laboratory Studies.—The blood count showed 68 per cent hemoglobin; 3,340,000 erythrocytes and 8,000 leukocytes, with 68 per cent neutrophils, 30 per cent lymphocytes and 2 per cent monocytes. The urine was normal, with a specific gravity

of 1.022. The Wassermann and Kahn tests of the blood gave negative reactions. Serum calcium was 11.8 mg.; serum phosphorus, 3.25 mg., and serum acid phosphatase, 5.5 units, per hundred cubic centimeters. In roentgenograms of the skull (fig. 1) there was a large area of increased density on the left side of the vertex. On its superior surface this abnormal mass appeared to invade the calvaria at several sites; its other surfaces were clearly outlined, scalloped and rounded. There was a definite increase in the digital markings; the suture lines were not separated. The sella turcica was normal in size; the dorsum sella was intact; the left anterior clinoid process was eroded. The interpretation was that of a tumor of the left hemisphere with evidence of increased intracranial pressure. The electroencephalogram revealed high voltage, slow waves of 2 to 3 per second frequency over the frontal lobes and over the left parietal area in grounded leads. In push-pull tracings there was out of phase activity over the parietal and frontal areas on the left side; these were high voltage, slow waves, which were so sharply demarcated at times as to be paroxysmal and were noted in coronal, parasagittal and diagonal tracings. There was also slight out of phase activity over the right parietal region. These findings indicated a focal lesion of the left parietal lobe with paroxysmal features.

Course of Illness.—The progressive history of sensorimotor jacksonian seizures, the clinical signs and the confirmatory laboratory studies indicated a brain tumor involving the left sensorimotor area. At operation, Dr. Rudolph Jaeger found that the tumor had penetrated the dura and eroded the calvaria near the midline. The mass beneath the dura was tense and calcified with a great deal of fibrosis around it, and had the appearance of a dense meningioma attached to the superior longitudinal sinus. The calcified tumor was approximately 3 inches (7.5 cm.) in length and 2 inches (5 cm.) in diameter; it was removed *en masse*. Extending from the anterior part of this mass and occupying the whole of the anterior fossa on the left was a huge boggy meningioma, which was not grossly calcified. Removal of these two masses left a strip of tumor, approximately ¾ inch (1.9 cm.) in diameter, along the superior longitudinal sinus; this was completely removed at a subsequent operation.

The patient was discharged on April 30. Her neurologic status at that time was unchanged except in the following respects: She was clearer mentally. The papilledema had disappeared, so that there was only slight indistinctness of the margins of the optic disks. Hearing was definitely improved, but bone conduction remained better than air conduction. The extraocular pareses persisted as before operation. The right upper and lower limbs, which had become paralyzed during operation, were rapidly returning to normal.

Pathologic Report.—Gross Description: The tumor consisted of two firm, lobulated hemispherical masses, the diameter of one being 8.5 cm. and that of the other 5.5 cm. (fig. 2). The surface of these masses was smooth and covered by a thin layer of fibrous tissue, from which septums divided the tumor into lobules. The inner surface was trabeculated, with radiating lines running from independent centers for each lobule. The tissue had a gritty feel when cut, and was composed in large part of calcified material. In addition to these two large masses, there were numerous small, firm pieces of tissue, also gritty to the touch, which had been removed with the electric loop. These formed a grapelike cluster, which, when reassembled, measured 16 by 13.5 cm. The entire tumor weighed 273 Gm. There were also five small bone fragments taken from the portion of the skull overlying the tumor.

Microscopic Description: The tumor was surrounded by a thin, closely adherent capsule composed of fibrous tissue and containing many young blood vessels and several medium-sized veins. Short trabeculae were seen penetrating from the capsule into the substance of the tumor. The cellular portion of the tumor consisted of a dense fibroblastic tissue with a heavy collagenous stroma. The cells were composed typically of an oval or elongated nucleus with a distinct nuclear

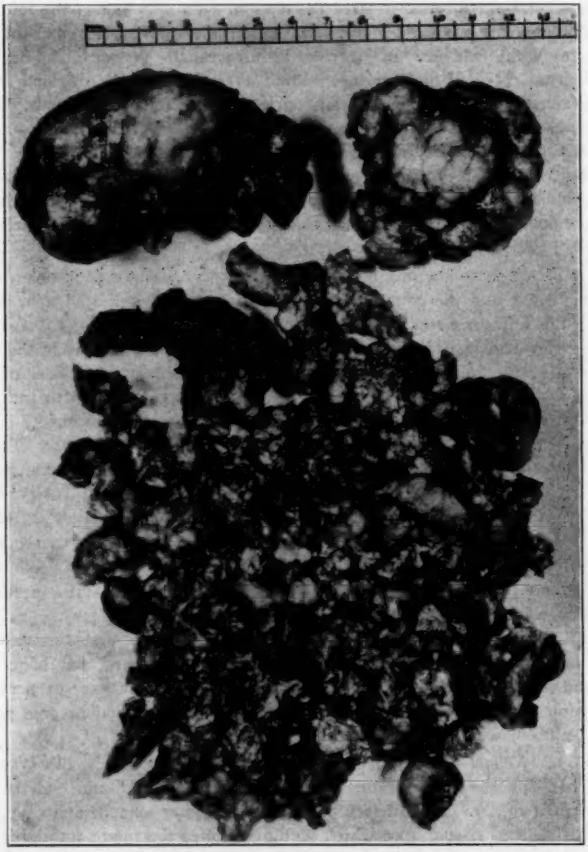

Fig. 2.—Gross appearance of the tumor. The two hemispherical masses, which were almost entirely ossified, are in the upper portion. The small pieces of tissue have been reassembled below.

membrane, containing sparse, coarsely granular chromatin, in an indistinct cytoplasm. These cells were arranged in sheets and whorls, and the typical streaming formation of the cells could be easily seen (fig. 3). Although the tumor was relatively avascular, many young blood vessels could be seen. Some sections of the specimen were made up of the typical cellular elements alone, but most contained

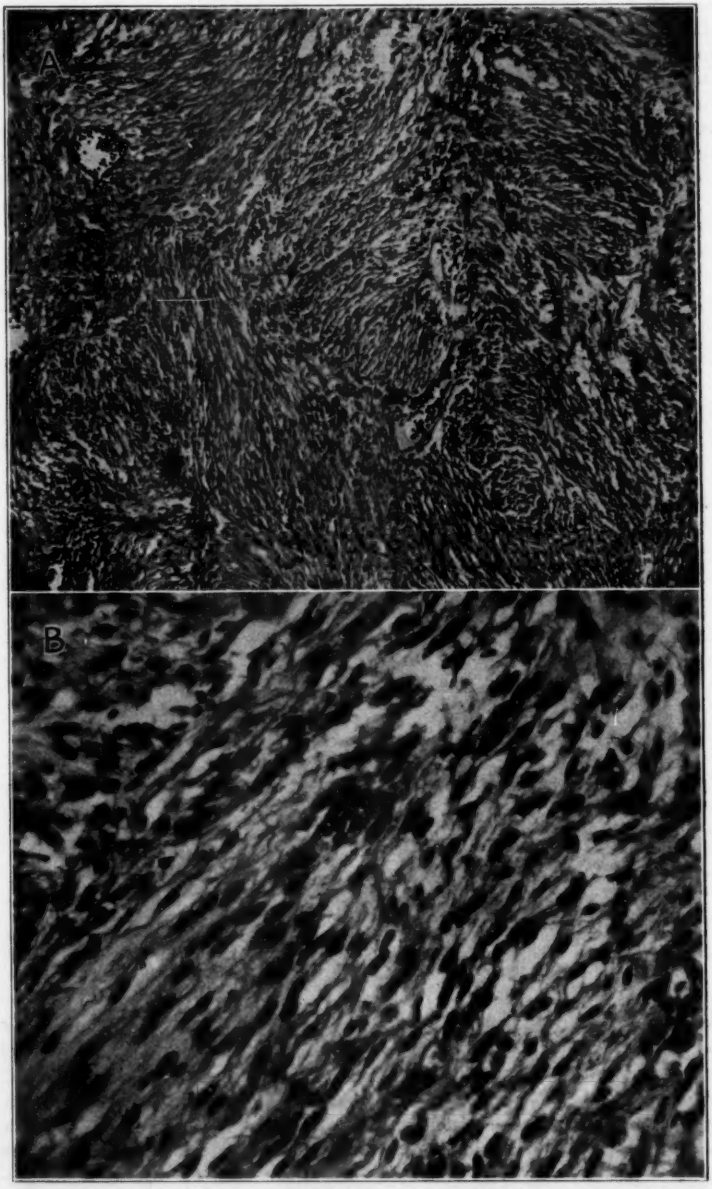

Fig. 3.—Photomicrographs showing the structure of the cellular portion of the tumor. *A*, low power view (× 100) demonstrating the streaming of the cell; *B*, high power view (× 400) of the cells showing the oval nuclei and indistinct cytoplasm.

bone fragments. These were scattered in irregular fashion throughout the sections. They were of various sizes and shapes, ranging from very small circular fragments to large irregular plates, completely filling a low power field (fig. 4). The smaller segments were homogeneous, dark-staining masses surrounded by the tumor cells. The larger osseous plates were composed of portions of dark, but irregularly staining, tissue, appearing as though it was made up of many smaller segments fused together. The edges of the solid portion extended into the surrounding cellular tissue like many tentacles, but was sharply demarcated from the

Fig. 4.—Appearance of the bone within the tumor; × 35.

tumor itself by its much darker color and lack of cellularity. Both osteoblastic and osteoclastic activity could be seen (fig. 5). Some sections of the tumor were completely contained within such bridges of membranous osseous tissue; others were filled with small separate islands of bone, lying in a matrix of tumor cells. Some of the fragments of bone were near the surface of the tumor, but none appeared connected to the fibrous tissue capsule. In addition to the bone, there were many small calcium deposits in some sections of the tumor. The fragments of bone from the skull contained no tumor cells and were typical in structure.

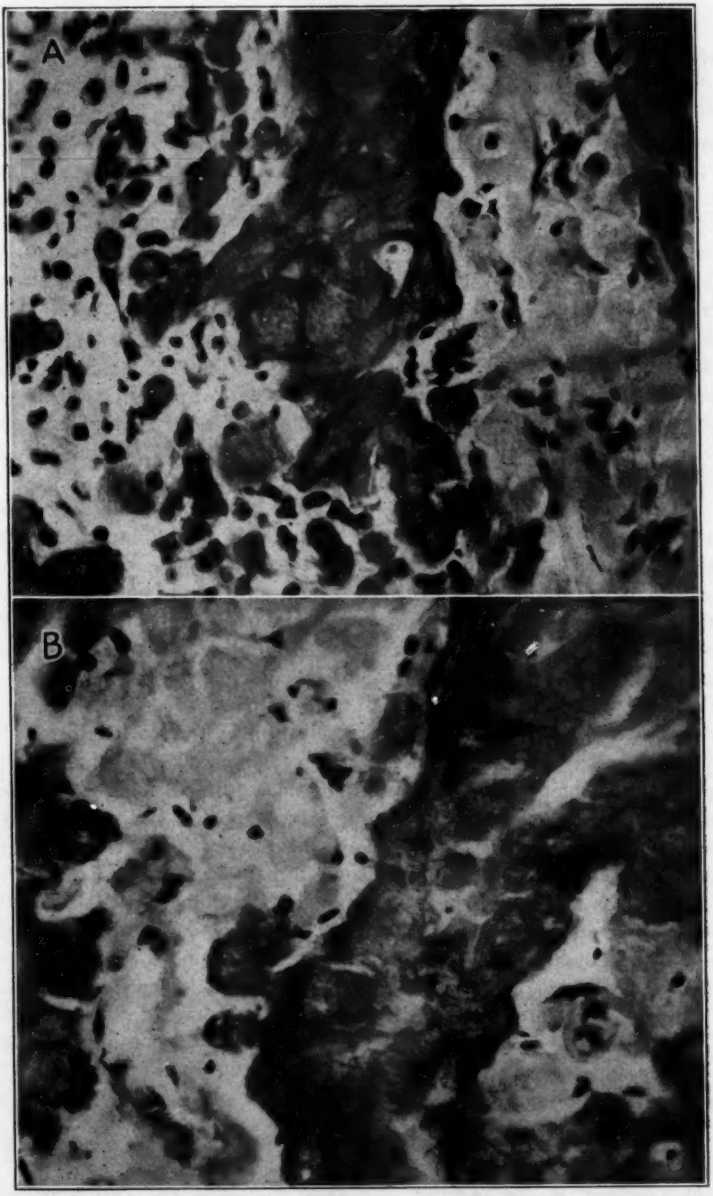

Fig. 5.—Photomicrographs of the structure and the cellular reaction around the osseous tissue; × 400. *A*, small, isolated islets of bone surrounding a larger portion; *B*, osteoblastic and osteoclastic activity at the edges of the bone.

COMMENT

The presence of bone formation within meningiomas has aroused speculation as to the origin of the osseous tissue. Although few authors have written on the subject, at least three possibilities have been discussed, either directly or by implication: The formation of bone is secondary to degeneration of the tumor cells (Bailey [3]; Courville and Abbott [4]; Gray [7]); the bone comes from the overlying skull (Courville and Abbott [4]; Bailey [3]; Cushing and Eisenhardt [2]); the bone is formed by the multipotential cells which make up the tumor itself (Globus [5]; Cushing and Eisenhardt [2]; Alpers [9]). Since the tumor is derived from the primitive meningeal material, which incorporates in itself the primordium of the several layers of the mature meninges, as well as that of the periosteum, it is reasonable to assume that the meningioma is likely to acquire the character of any one of the component layers, including occasionally bony structures traceable to the periosteal anlage in the skeletoneural intertissue.[5] The potentialities of meningiomatous cells have been described fully in a recent paper by Freedman and Forster.[10]

It is not possible from this one case to determine the source of osseous tissue within meningiomas. Although this tumor contained calcium deposits, the first theory does not seem adequate, as it does not explain the source of the fibroblasts which cause the ossification. It is difficult to accept the origin of osteoblasts from necrotic cells. The second consideration is ruled out by the location of the bone within the tumor and the absence of endosteal projections from the surface. Moreover, this tumor eroded the skull rather than caused hyperostosis. Although it is tempting to say that the youth of this patient fits well with the theory of multipotentiality of developing cells, and that therefore early in their development some of them formed bone within the tumor, the other osteoblastic meningiomas reported occurred in the fourth and fifth decades of life. Nevertheless, the third theory seems the most likely explanation for the bone formation.

The gross and microscopic appearance of this tumor was typical of the descriptions given for this type by Cushing and others. Some of the small islands of bone appeared almost cartilaginous, but this was due in part to the decalcifying process. As the formations were arranged, it appeared as though isolated islands of bone were formed, and many of these coalesced to form larger fragments. There was nothing unusual about the appearance of the cellular portion of the tumor, the arrangement and type of cell being typical.

9. Alpers, B. J.: Cerebral Osteochondroma of Dural Origin, Ann. Surg. **101**:27, 1935.

10. Freedman, H., and Forster, F.: Bone Formation and Destruction in Hyperostoses Associated with Meningiomas, J. Neuropath. & Exper. Neurol. **7**:69, 1948.

The duration of this child's symptoms should be mentioned. Cushing described the osteoblastic meningioma as slow growing, and the duration of symptoms in his cases ranged from one to twelve years, the patients at operation being 36 to 54 years of age. Our patient's symptoms began when she was 4 years old and had been present for eight years when she came to the hospital.

SUMMARY

The case of a 12 year old girl with an osteoblastic meningioma is reported. Symptoms began when she was 4 years old with seizures. Later, neurologic signs indicating a tumor involving the left sensorimotor area developed. Roentgenograms of her skull showed a huge calcified mass in this region. At operation an osteoblastic meningioma, weighing 273 Gm., was removed. Microscopic examination revealed typical membranous bone formation within the tumor. The possibilities of the origin of the osseous tissue are discussed. The most likely explanation is that the bone is laid down by the tumor cells themselves.

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INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM IN INFECTIOUS MONONUCLEOSIS

Report of a Case with Ataxia and Nystagmus

ROBERT M. HOYNE, M.D.
URBANA, ILL.

MORE THAN fifty years ago Pfeiffer [1] described the first case of infectious mononucleosis and called it "glandular fever." This disease usually affected children and young adults and consisted of fever, inflamed throat, cervical lymphadenopathy, hepatomegaly and splenomegaly, with eventual recovery. In 1923 Downey and McKinlay [2] first described the characteristic blood picture and the "atypical lymphocytes" found in infectious mononucleosis. By careful study of blood smears it thus became possible to differentiate the benign infectious mononucleosis from leukemia. In 1932 Paul and Bunnell [3] noted that the blood of patients with infectious mononucleosis contained antibodies capable of agglutinating sheep cells. Refinement of this "heterophil antibody test" [4] provided a valuable diagnostic procedure for recognition of this disease.

The clinical picture of infectious mononucleosis is now well recognized.[5] The patients are usually of a younger age group, and the two sexes are affected equally. The symptoms and signs of this febrile systemic illness vary considerably. Coogan and associates [6] mentioned the following cardinal signs: (1) fever with or without chills, (2) sore throat, (3) headache, (4) enlarged cervical glands (or, more rarely, axillary or inguinal adenopathy) and (5) enlarged spleen. Other symptoms less frequently encountered are cutaneous rashes of the maculopapular or morbilliform type, chronic cough due to enlarged mediastinal glands, and hepatic involvement with or without jaundice.

From the Division of Internal Medicine, Carle Memorial Hospital and Carle Hospital Clinic.

1. Pfeiffer, E., cited by Coogan, T. J.; Martinson, D. L., and Mathews, W. H.: Illinois M. J. **87**:296, 1945.

2. Downey, H., and McKinlay, C. A.: Acute Lymphadenosis Compared with Acute Lymphatic Leukemia, Arch. Int. Med. **32**:82 (July) 1923.

3. Paul, J. R., and Bunnell, W. W.: Presence of Heterophile Antibodies in Infectious Mononucleosis, Am. J. M. Sc. **183**:90, 1932.

4. Davidsohn, I.: Serologic Diagnosis of Infectious Mononucleosis, J. A. M. A **108**:289 (Jan. 23) 1937.

5. Bernstein, A.: Infectious Mononucleosis, Medicine **19**:85, 1940.

6. Coogan, T. J.; Martinson, D. L., and Mathews, W. H.: Neurological Symptoms of Infectious Mononucleosis, Illinois M. J. **87**:296, 1945.

The clinical diagnosis of infectious mononucleosis is confirmed by the presence of the "atypical lymphocytes" in the blood smear and the positive heterophil agglutination reaction. The course of the illness is usually from one to four weeks, with complete recovery. However, fatalities have been noted, and in a review of 500 cases Thomsen and Vimtrup [7] described 4 instances of death, apparently due to respiratory paralysis.

Complications of infectious mononucleosis involving the central nervous system appear rarely but have been recognized since the first reports, in 1931, of Johansen [8] and Epstein and Dameshek.[9] Various neurologic signs and symptoms have been reported. There may be a varying degree of clouding of the sensorium, ranging from mild lethargy to coma.[4] Toxic psychosis resembling schizophrenia has recently been noted.[10] Slade[11] collected 32 cases with involvement of the central nervous system and found the two commonest symptoms to be headache (30 cases) and stiffness of the neck (17 cases). However, the presence of headache does not always signify neurologic involvement. Press and co-workers [12] found this symptom in 34 of 96 apparently uncomplicated cases of infectious mononucleosis. Signs of meningeal irritation are common, with stiffness of the neck, opisthotonos and Kernig and Brudzinski signs. Photophobia, nystagmus, and poor articulation may occur.[13] Various cranial nerves may be involved, with resulting anosmia,[14] optic neuritis,[15] paralyses of the extraocular muscles [16] and facial palsy.[15]

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7. Thomsen, S., and Vimtrup, B.: Six Fatal Cases of Infectious Mononucleosis Complicated by Central Respiratory Paralysis, Nord. med. (Hospitalstid.) **4**:3295, 1939.

8. Johansen, A. H.: Serous Meningitis and Infections Mononucleosis, Acta med. Scandinav. **76**:269, 1931.

9. Epstein, S. H., and Dameshek, W.: Involvement of Central Nervous System in Case of Glandular Fever, New England J. Med. **205**:1238, 1931.

10. Raymond, R. R., and Williams, R. L.: Infectious Mononucleosis with Psychosis: Report of a Case, New England J. Med. **239**:542, 1948.

11. Slade, J. de R.: Involvement of Central Nervous System in Infectious Mononucleosis: Report of Two Cases, New England J. Me .. **234**:753, 1946.

12. Press, J. H.; Shlevin, E. L., and Rosen, A. P.: Infectious Mononucleosis: Study of Ninety-Six Cases, Ann. Int. Med. **22**:546, 1945.

13. Marshall, E. A.: Infectious Mononucleosis, Am. J. Clin. Path. **9**:298, 1939.

14. Marshal, Bargeton and Mahoukau, cited by Bernstein.[5]

15. Gsell, O.: Meningitis serosa bei Pfeifferschem Drüsenfieber (Mononucleosis infectiosa), Deutsche med. Wchnschr. **63**:1759, 1937.

16. Epstein and Dameshek.[9] Fledelius, M.: Augenmuskellähmung als Komplikation der Mononucleosis infectiosa, Acta ophth. **13**:150, 1935. Vaughan, S. L.; Regan, J. S., and Terplan, K.: Infectious Mononucleosis Complicated by Spontaneous Rupture of the Spleen and Central Nervous System Involvement, Blood **1**:334, 1946.

Ashworth and Motto recently reported the first case of infectious mononucleosis complicated by bilateral papilledema.[17]

No characteristic changes in the cerebrospinal fluid are found in these cases of infectious mononucleosis. The pressure may be elevated, and pleocytosis is often observed, most of the cells being lymphocytes. A case reported by Thelander and Shaw[18] showed 730 cells per cubic millimeter of spinal fluid. The protein of the fluid is usually increased; the Pandy test for globulin may give a positive reaction; the Wassermann reaction is negative, and the colloidal gold curve is normal.

Spinal fluid determinations should probably be made in all cases of infectious mononucleosis with moderate or severe headache. Schmidt and Nyfeldt[19] found abnormal spinal fluids in 4 cases without cerebral symptoms and suggested that a spinal puncture be performed routinely in all cases of infectious mononucleosis.

Nystagmus and ataxia are not common in cases of infectious mononucleosis with involvement of the central nervous system.[20] A recent review of the literature[11] mentioned only 3 cases with nystagmus and 3 with ataxia. Because of the rarity of these signs, the following case is reported.

REPORT OF CASE

A white youth aged 20, a college student, had always been well until the latter part of October 1947, when there developed fever, headache, dizziness, sore throat and cervical lymphadenopathy, necessitating his hospitalization elsewhere. Hepatomegaly, splenomegaly and generalized lymphadenopathy had been observed, and blood counts had revealed leukocytosis, with a marked predominance of lymphocytes and monocytes. The attending physician made a diagnosis of infectious mononucleosis, and the patient was given parenteral injections of penicillin, as well as symptomatic treatment. A significant degree of vertigo and ataxia persisted, and the patient registered at the Carle Hospital Clinic for further study on Nov. 12, 1947.

Physical examination showed a rather pale, well nourished young man in no acute distress. He had lost about 10 pounds (4.5 Kg.) during his recent illness. The blood pressure measured 120 mm. of mercury systolic and 80 mm. diastolic. No significant abnormalities were noted in the physical examination. The liver and spleen were no longer palpable, and adenopathy had completely disappeared. Neurologic examination showed the gait to be ataxic and the Romberg sign

17. Ashworth, J., and Motto, S. A.: Infectious Mononucleosis Complicated by Bilateral Papilloretinal Edema: Report of a Case, New. England J. Med. **237**:544, 1947.

18. Thelander, H. E., and Shaw, E. B.: Infectious Mononucleosis, with Special Reference to Cerebral Complications, Am. J. Dis. Child. **61**:1131 (June) 1941.

19. Schmidt, V., and Nyfeldt, A.: Ueber Mononucleosis infectiosa und Meningoencephalitis, Acta oto-laryng. **26**:680, 1938.

20. Landes, R.; Reich, J. P., and Perlow, S.: Central Nervous System Manifestations of Infectious Mononucleosis: Report of Case, J. A. M. A. **116**:2482 (May 31) 1941.

slightly positive. A fine nystagmus was present on lateral gaze in either direction, but the eyes were otherwise normal. The rest of the neurologic examination showed nothing remarkable.

The urine was normal. The hemoglobin measured 13.8 Gm. per hundred cubic centimeters of blood. The erythrocyte count was 4,550,000 and the leukocyte count 8,000 per cubic millimeter. The differential study revealed 13.5 per cent polymorphonuclear leukocytes, 79.5 per cent lymphocytes, 5 per cent monocytes and 2 per cent eosinophils. Numerous "atypical lymphocytes" were present. Routine Kline and Kahn tests gave negative results, and the sedimentation rate of the erythrocytes measured 8 mm. in forty-five minutes by the Westergren technic. The blood urea was 32 mg. per hundred cubic centimeters. Roentgenograms of the skull and chest showed no abnormality. Heterophil antibody studies of the uncentrifuged blood serum showed agglutination in a dilution of 1:256. The centrifuged serum was positive in a dilution of 1:2,048.

Spinal puncture was performed on November 19, about three weeks after the onset of the illness. The pressure was normal; the protein was 79 mg. per hundred cubic centimeters of cerebrospinal fluid, and the Pandy reaction for globulin was positive. The cell count was 6 per cubic millimeter of fluid, 2 of which were polymorphonuclear leukocytes and 4 lymphocytes. The Kahn reaction of the cerebrospinal fluid was negative, and the colloidal gold curve was reported as 0011210000.

A diagnosis of infectious mononucleosis with complications referable to the central nervous system was made. The patient was advised not to go to school temporarily and was reassured that eventual recovery was likely. Multiple vitamins and nicotinic acid, to be taken orally, were prescribed. By December 1 the patient still exhibited nystagmus and ataxia. The leukocyte count was 5,300 per cubic millimeter of blood, with 41.5 per cent polymorphonuclear leukocytes, 57.5 per cent lymphocytes and 1 per cent monocytes. The heterophil antibody test gave a positive reaction in the uncentrifuged serum to a dilution of 1:128 and in the centrifuged serum in a dilution of 1:512. He was hospitalized from December 1 to December 7 for observation and treatment. During this period a daily intravenous infusion of 2.75 mg. of histamine diphosphate diluted with 250 cc. of isotonic sodium chloride solution U. S. P. was given, and considerable symptomatic improvement was observed. The exact role of the histamine in producing the improvement is difficult to evaluate. By December 20 the ataxia had disappeared, but slight nystagmus persisted, and the patient was allowed to resume normal activities. On March 29, 1948, the leukocyte count was 4,650 per cubic millimeter of blood, with 50 per cent polymorphonuclear leukocytes and 50 per cent lymphocytes. Both the ataxia and the nystagmus had disappeared, and the patient was asymptomatic.

The patient was examined in a routine check-up on Jan. 7, 1949. During the preceding year he had married and had played college football. Physical and neurologic examinations showed a normal condition. The leukocyte count was 6,700 per cubic millimeter of blood, with 54 per cent lymphocytes, 38.5 per cent polymorphonuclear leukocytes, 1 per cent monocytes and 5.5 per cent eosinophils. Lymphocytosis was prominent more than one year after the original illness, and the heterophil antibody reaction of the uncentrifuged serum was positive in a dilution of 1:8.

COMMENT

The diagnosis of infectious mononucleosis was certain in this case in view of the fever, lymphoid hypertrophy, abnormal lymphocytes in

increased number and high titer of the heterophil antibody reaction. The findings in the cerebrospinal fluid were not remarkable, the only abnormality being an increase in the protein content. A spinal puncture done at the peak of the disease, rather than three weeks later, might have revealed more striking changes. In the present case, the patient had recovered from the fever, prostration and lymphadenopathy within three weeks. However, he remained incapacitated by ataxia and nystagmus, and eight weeks elapsed before these neurologic manifestations disappeared completely.

SUMMARY

A case is reported in which infectious mononucleosis was complicated by involvement of the central nervous system, causing ataxia and nystagmus. Recovery was complete.

Almost any combination of neurologic signs and symptoms can occur when the central nervous system is affected by this disease. This diagnostic possibility must be considered in any acute or subacute neurologic disorder; cerebrospinal fluid determinations and heterophil antibody studies should be made more frequently in these cases.

NEUROLOGIC CONDITIONS OCCURRING AS COMPLICATIONS OF PREGNANCY

ARTHUR B. KING, M.D.
Neurosurgeon, Guthrie Clinic
SAYRE, PA.

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Summary

CONDITIONS DUE TO DRUGS

HEMORRHAGIC ENCEPHALOPATHY DUE TO TREATMENT WITH ARSPHENAMINE IN PREGNANCY

Cole [51] stated that young adults are more susceptible to toxic effects of arsenical drugs than older persons and that women are more sensi-

51. Cole, H. N., and others: Toxic Effects Following Use of Arsphenamine, J. A. M. A. **97**:897 (Sept. 26) 1931.

tive than men. Ingraham [52] collected figures to show that the state of pregnancy also increases the incidence of untoward reactions. He stated that in a series of 6,431 injections of arsphenamine in syphilitic women who were not pregnant at the time there were 15.7 mild reactions and 2.0 severe reactions per thousand injections, whereas in a series of 6,345 injections in pregnant women there were 34.4 mild reactions and 3.0 severe reactions per thousand injections. Among the severe reactions to arsphenamine, hemorrhagic encephalopathy accounts for perhaps two thirds of the deaths. A number of authorities, including Plass and Woods,[53] Moore,[54] Ingraham,[52] Cormia [55] and McKelvey and Turner,[56] stated the belief that pregnancy increases the incidence of this condition. Hemorrhagic encephalopathy is most likely to occur after the second or third injection. It scarcely ever occurs after six injections have been given. It is believed that arsenical treatment during the last trimester is more dangerous than treatment in the first few months. Phelps and Washburn [57] are authority for the statement that 1 death from hemorrhagic encephalopathy occurs for every 1,171 patients treated.

The onset of symptoms is almost invariably within seventy-two hours after the last injection has been given. It may be marked by headache, vertigo, nausea, vomiting and fever. Often the patient is so apprehensive and disturbed that the examiner may suspect an emotional disorder. Such symptoms have been termed prodromes. After several hours convulsions begin. These may be general or focal, and in some instances there are also muscular twitchings. The convulsions are followed by stupor or coma. At first, the patient may be rigid, and the tendon reflexes may be brisk. Later, as collapse ensues, there are often general flaccidity of the muscles and loss of tendon reflexes. The plantar responses are usually of extensor type or absent. There is retention of urine in many instances. Hemiplegia, or more often paraplegia, may be demonstrated. Cyanosis is an ominous sign and occurs in a large percentage of patients before death. At least 50 per cent of patients die within twenty-four to seventy-two hours afer the onset.

52. Ingraham, N. R., Jr.: Complications Due to Arsenical Therapy in Syphilitic Pregnant Women, J. A. M. A. **112**:1537 (April 22) 1939.

53. Plass, E. D., and Woods, E. B.: Hemorrhagic Encephalitis (Neoarsphenamine) in Obstetric Patients, Am. J. Obst. & Gynec. **29**:509, 1935.

54. Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., Charles C Thomas, Publisher, 1943, p. 480.

55. Cormia, F. E.: Hemorrhagic Encephalitis from Neoarsphenamine in Pregnancy, Canada M. A. J. **35**:610, 1936.

56. McKelvey, J. L., and Turner, T. B.: Syphilis and Pregnancy, J. A. M. A. **102**:503 (Feb. 17) 1934.

57. Phelps, J. R., and Washburn, W. A.: Toxic Effects of Arsenical Compounds Employed in the Treatment of Syphilis in the United States Navy, U. S. Nav. M. Bull. **28**:659, 1930.

Postmortem examination reveals that the brain is intensely congested and edematous. On section, one sees innumerable petechial hemorrhages, which are found on microscopic examination to be ring hemorrhages surrounding the small blood vessels. Hyaline thrombi are sometimes seen in the small vessels but are not essential for the production of the lesions. The same changes are found in the brain stem and the spinal cord.

Hemorrhagic encephalopathy is believed to be due to a toxic effect on the endothelium of the blood vessels, which leads to leakage of the red cells into the tissues. There is evidence that this phenomenon is one of sensitization. It is clear that syphilis plays no part, since the condition may occur in nonsyphilitic women.

If the patient survives, residua are often found. In my experience, the end result has usually been spastic paraplegia with ataxia, mild reduction of sensibility and difficulty in control of the bladder. There may also be persistent mental disturbances.

Since this condition is associated with convulsions and coma and may occur during the last trimester, it may be mistaken for eclampsia. The absence of edema, hypertension and albuminuria and the history of an injection of arsphenamine within seventy-two hours usually make the differential diagnosis evident.

CEREBRAL DAMAGE DUE TO GENERAL ANESTHESIA

It has long been known that in rare instances general anesthesia may be followed by convulsions and by coma, but it was not until 1936, when Courville's [58] paper appeared, that any extensive study was made of this problem. Courville published his experiences with 13 cases of this condition and found 6 additional cases previously described in the medical literature. In all these cases nitrous oxide was the anesthetic employed, and in all there was evidence of serious damage to the brain. Since in 4 of the series of 13 cases the convulsions occurred during delivery, or immediately after delivery, when the anesthetic was given during repair of the perineum, one might well suspect that pregnant women are especially susceptible to this reaction. In the case reported by Yaskin [59] the cerebral damage was also a result of nitrous oxide anesthesia during delivery of a previously healthy young woman.

The duration of anesthesia is apparently not important, for in most cases the anesthesia was brief, often lasting only ten or twelve minutes.

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58. Courville, C. B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129, 1936.

59. Yaskin, J. C.: Nonsuppurative, Nonepidemic Encephalitis Following Labor and in the Puerperium: Report of a Case Probably Due to Cerebral Anoxemia, with Review of Literature, Arch. Neurol. & Psychiat. **26**:371 (Aug.) 1931.

The operation was sometimes a minor one, such as removal of tissue for biopsy, uterine curettage, extraction of a tooth or normal delivery. In 8 instances there was sudden failure of respiration, and in 4 cases the pulse became very feeble or imperceptible. In 4 cases, however, no alteration of pulse or respiration and no cyanosis was noted during the anesthesia. In all cases, when the anesthetic was withdrawn the patient remained in deep coma. Respiration was irregular at this time, and the temperature was elevated. Convulsions, either general or focal, developed in a large percentage of cases, and generalized muscular rigidity was sometimes seen. Most of the patients died in two to seven days without regaining consciousness. Terminal hyperpyrexia was common.

Of the patients who survived, some made a rapid and complete recovery. Others, however, displayed permanent mental or physical disorders which pointed unmistakably to injury of the brain. Dementia of variable degree seems to have been the most frequent sequel. Disturbances of speech and loss of control of the emotional reactions have been mentioned. Defects in the visual fields suggestive of cortical damage were observed several times. There was also ataxia of cerebellar type, and in some instances signs referable to the basal ganglia, such as athetosis, myoclonus and parkinsonian syndromes, were noted. I have studied a patient who exhibited aphasia, apraxia, reduction of vision without changes in the optic nerve heads, and cerebellar ataxia. All the signs disappeared after a few weeks except for the reduction of vision and the ataxia.[58]

Courville[58] and Löwenberg and associates[60] both described the anatomic changes in the brain. The most destructive lesions were observed in the cerebral cortex, and these were usually diffuse or disseminated. The distribution was not always the same, for in some instances the frontal lobes were most severely affected and in others the occipital lobes. Areas of necrosis were also noted in the lenticular nuclei and in the cortex of the cerebellum. The subcortical white matter, the various structures of the brain stem, the spinal cord and the spinal nerves seem to have escaped. Four types of damage were observed in the cerebral cortex: (1) degeneration of individual cells; (2) small focal areas of vacuolation and rarefaction of the tissues; (3) zonal necrosis in the cortex, and (4) complete disintegration of the cortex, which seemed to be a more advanced stage of the zonal necrosis. Courville stated the belief that the essential cause of these lesions is asphyxia and that the nitrous oxide does not contribute any toxic effect.

60. Löwenberg, K.; Waggoner, R., and Zbinden, T.: Destruction of the Cerebral Cortex Following Nitrous Oxide Anesthesia, Ann. Surg. **104**:801, 1936.

Occasionally anesthetics other than nitrous oxide seem to produce similar effects. Thus, Weber [61] reported a case in which extensive cerebral damage followed the use of ether anesthesia, and I have observed a similar case in which cortical blindness was left as a permanent residuum. Steegmann [62] and Gebauer and Coleman [63] described cerebral damage following the use of cyclopropane, and Steegmann mentioned a case in which tribromoethanol solution U. S. P. (avertin in amylene hydrate®) was responsible.

Recently I have observed a patient, aged 38, who had marked cerebral changes following the use of thiopental sodium U. S. P. (pentothal sodium®) during delivery. The patient had a laryngeal spasm and later vomited and aspirated the material, obstructing her trachea. Before an airway could be restored, an anoxemia was profound. The history is summarized.

After a normal prenatal course, the patient was taken to the delivery room and placed in the dorsal lithotomy position. Twenty cubic centimeters of 2.5 per cent thiopental sodium was given between 6:01 and 6:05 a. m., when a normal child was delivered. The state of anesthesia is said to have been light.

At this time, she vomited and aspirated the vomitus. She was placed in the Trendelenburg position, and suction was carried out. Respiratory exchange was poor, and, despite a nasal airway, oxygen could not be forced into the lungs. Cyanosis became marked. A tracheotomy was started at 6:15 a. m. and was completed at 6:25 a. m. A large amount of spinach was removed from the larynx. The anesthetist stated that there was no laryngeal spasm.

By this time the patient was deeply unconscious. Generalized rigidity followed shortly after this. About two hours later intermittent extensor spasms were noted in all her limbs. Three hours after the accident, she responded slightly to very painful stimuli. The pupils were widely dilated and reacted very slightly to light. There was marked narrowing of the retinal vessels. Both the arms and the legs were held in extension. The tendon reflexes were hyperactive, and both plantar responses were extensor.

At the end of eight hours the patient had aroused sufficiently to open her eyes on command. An occasional word was spoken. The pupils still barely reacted to light, and she would not follow a light. Pinprick caused a withdrawal response, and the extensor rigidity was gone. Weakness of the left arm and leg was noted. She licked her lips constantly. The right plantar response was now of flexor type.

On the following day the state of consciousness had improved considerably but memory was almost nil. It was thought that she was still blind. The weakness of the left arm and leg had disappeared.

Three days after the onset of symptoms, she conversed clearly, but there was marked clouding for time and place. Recent memory was very poor. A slight sensory aphasia was present. All the tendon reflexes were hyperactive, but the pathologic reflexes had disappeared.

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61. Weber, F. P.: Complete Mindlessness and Cerebral Diplegia After Status Convulsivus Associated with Aether Anesthesia, Brit. J. Child. Dis. **28**:421, 1931.

62. Steegmann, A. T.: Encephalopathy Following Anesthesia: Histologic Study of Four Cases, Arch. Neurol. & Psychiat. **41**:955 (May) 1939.

63. Gebauer, P. W., and Coleman, F. P.: Postanesthetic Encephalopathy Following Cyclopropane, Ann. Surg. **107**:481, 1938.

By the fourth postpartum day she could read a few large letters, but vision remained poor. The general state of consciousness continued to improve. A detailed ophthalmologic examination on the ninth postpartum day showed vision of 20/200 in each eye. The peripheral and central fields were full. The fundi were normal. It was thought that she had cortical blindness. Two days later, however, vision was 2/100 in the right eye and 20/70 in the left eye. She could also pick out an occasional word in Jaeger type 4. A honomymous field defect was found in the right lower nasal and the left lower temporal quadrant. By the twenty-first postpartum day vision was 20/30 in each eye, but the field defects persisted.

At this time, most of her neurologic defects had cleared. Recent memory was still poor. All the cranial nerves were intact. Motor power and tone were good, but fine movements were not as precise as they should have been. Sensory tests were well performed, but mistakes were made in laterality. Definite apraxia was present, and some of her reading difficulties were thought to be due to aphasia.

Comment.—The patient showed widespread cerebral damage, which was mainly reversible except for some of the higher functions. It would appear that a combination of thiopental anesthesia and anoxemia was responsible. I have not observed this precise picture with anoxemia alone.

INTOXICATION DUE TO SULFONAMIDES

It is well known that the sulfonamides may cause serious intoxications. Polyneuritis has been reported many times, and encephalopathy has been observed. Since these drugs are frequently given during pregnancy for gonorrhea and pyelitis and after delivery for pelvic infection, mastitis and numerous other bacterial diseases, it is necessary to mention the untoward effects. Only the neurologic complications will be discussed.

Among the first to note involvement of the central nervous system were Fisher and Gilmour [64] who described the case of a woman who had been treated for fifteen days with sulfanilamide for lupus erythematosus. There occurred at the end of this time a sudden rise of temperature to 104.3 F. and ascending paralysis, the latter proving fatal in three days. Necropsy revealed petechial hemorrhages in the brain, as well as the spinal cord, and perivascular degenerations and focal softenings independent of the hemorrhages. Roseman and Aring [65] reported the case of a man who received 112 Gm. of sulfamethylthiazole (4-methyl-2-sulfanilamidothiazole) in five days for pneumonia. He then had nausea, vomiting and amblyopia and became stuporous. The next day he had three convulsions and died. The temperature was not significantly elevated. Postmortem examination revealed small hemorrhages in the cerebral gray matter surrounding the capillaries. In

64. Fisher, J. H., and Gilmour, J. R.: Encephalomyelitis Following the Administration of Sulfanilamide, Lancet **2**:301, 1939.

65. Roseman, E., and Aring, C. D.: Encephalopathy Associated with Sulfamethylthiazole Therapy, New England J. Med. **224**:416, 1941.

addition, there were perivascular areas of necrosis. The epithelium of the small blood vessels was swollen and necrotic in some regions. These authors stated that the pathologic process was very similar to that seen in arsphenamine encephalopathy except that the hemorrhages were confined to the gray matter, whereas in the latter condition the hemorrhages are more numerous in the white matter than in the gray matter. Scheinker,[66] who reviewed this case and reported another of his own, attributed the lesions to vasospasm.

Garvin [67] treated a woman aged 37 with sulfamethylthiazole for pneumonia. On the seventeenth day of treatment, she had onset of hyperesthesia and tenderness of the legs. The drug was withdrawn, but on the next day she had a fever of 104 F. and fell into convulsions. Thereafter she was stuporous and died in three days. At autopsy no lesions could be discovered in the brain.

It will be noted that in these cases sulfamethylthiazole was usually responsible. Similar cases have been described in which sulfapyridine was used. It is clear that in most cases the drug has been administered in large doses, and often for more than two weeks. There seems to be no suggestion in the literature that pregnancy renders a patient more sensitive to such untoward effects. Nevertheless, we have observed 2 cases in which it is possible that pregnancy did play a role. These will now be given in brief.

A woman aged 19.[68] *Administration of sulfathiazole during labor to prevent infection and, again, on the ninth day post partum, followed by coma, rigidity, anuria and hyperpyrexia. Later development of flaccidity and ataxia, but reflexes brisk. Inability to talk for ten weeks and to walk for three months. Appearance of mental deterioration, euphoria and pronounced cerebellar ataxia after four months.*

A white woman aged 19 had an uneventful pregnancy, but at term it was thought necessary to induce labor. She made no progress toward delivery, however, and was brought to the hospital. There she was given 1 Gm. of sulfathiazole every four hours to prevent infection. About thirty-eight hours later the baby was born. On the fourth day post partum the mother began to vomit, and the drug, which had then been given for nearly six days, was withdrawn. Shortly afterward she began to have a low grade fever and showed signs of pelvic infection. Because of this, the sulfathiazole was given once more in the same dosage. On the next day, which was the ninth day after delivery, she was weak, listless and apprehensive. Her temperature rose to 104.6 F. The level of sulfathiazole in the blood was 11.5 mg. per hundred cubic centimeters. The drug was discontinued.

66. Scheinker, I. M.: Cerebral Vascular Changes Associated with Azosulfamide and Sulfamethylthiazole Therapy, J. Neuropath. & Exper. Neurol. **2**:301, 1943.

67. Garvin, C. F.: Peripheral Neuropathy and Toxic Psychosis with Convulsions Due to Sulfamethylthiazole, Am. J. M. Sc. **200**:362, 1940.

68. This case was reported previously by Luetscher, J. A., and Blackman, S. S.: Severe Injury to Kidneys and Brain Following Sulfathiazole Administration, Ann. Int. Med. **18**:741, 1943.

On the eleventh day the patient was comatose and appeared to be in shock. The temperature was 105 F., the pulse rate 172 and the respiration rate 36. The spinal fluid was entirely normal. On the following day she coughed up large amounts of frothy fluid. Her temperature had fallen to 101 F., and the pulse rate was 120 to 160 per minute. There were frequent vomiting and complete anuria. The nonprotein nitrogen content of the blood was 72 mg. per hundred cubic centimeters. A bright erythematous rash appeared over the face, neck, shoulders and thighs. She was still unconscious, and the only movements observed aside from those of respiration were the movements of the eyes. It was evident that the patient had sustained severe damage to the brain, kidneys and heart.

During the next few days, the temperature and pulse and respiration rates fell to normal levels, and urinary secretion was reestablished. However, the nervous symptoms persisted. There was generalized muscular rigidity, and at times rhythmic tremor of large amplitude involved the arms and the jaw. The cogwheel phenomenon was elicited at times. The jaws were widely open, and the tongue was stiffly protruded in an extraordinary fashion. No voluntary movements were observed. The tendon reflexes were all exaggerated and the plantar responses equivocal. The patient was incontinent and required tube feeding. At the end of the fourth week, she was still deeply stuporous.

At the end of the sixth week the patient was conscious but confused. She could move the legs feebly but had little power of movement in the arms. She could not talk or protrude the tongue. The extremities were now flaccid, but the tendon reflexes were brisk. The electroencephalogram showed large spikelike waves, of irregular form and with a rate of 5 per second. Biopsy of a muscle revealed a mononuclear reaction around the small arteries.

At the end of two months she could move all four extremities and even sit up, but could not talk. At the end of the tenth week she could form a few words imperfectly and had regained some strength and control of the right arm, whereas the left arm was still almost useless. The right calf was atrophic.

At the end of the third month she could walk with support.

Four months after delivery she was well nourished and, except for her neurologic status, appeared to be in good general condition. She displayed a childish euphoria not unlike that sometimes seen in multiple sclerosis. She did not seem distressed by her disability. Her memory was grossly deficient, and there was obvious deterioration. The cranial nerves were intact. Generalized muscular weakness was present but no actual paralysis. Her chief difficulty was profound cerebellar ataxia, which made it impossible for her to feed herself or to walk without support. Speech was slow and of scanning type. The tendon reflexes were normal and the plantar responses flexor. Psychometric examination gave an intelligence quotient of 57 per cent. She was discharged. I am informed that she has not improved since.

Negro girl aged 15. Administration of sulfathiazole on third and fourth days post partum. Development of mastitis on ninth day and the drug given again. On next day, stupor, temperature of 105 F. and pulse rate of 178. Later, confusion and paralysis of extremities. Slow improvement. At end of second month post partum, patient demented, could walk a little and articulate indistinctly.

A Negro girl of 15 passed through her first pregnancy without incident. On the third day post partum she had a slight fever and was given sulfathiazole for two days, the total dose being 12 Gm. On the ninth day, mastitis developed, and sulfathiazole was administered once more, in doses of 1.0 Gm. every four hours. On the next day she became delirious and rapidly passed into stupor. Her tem-

perature rose to 105 F. She vomited repeatedly. Administration of the drug was stopped. On the following day, i. e., on the eleventh day post partum, her temperature was still above 104 F., and she was brought to the hospital.

She was then confused and restless and apparently entirely out of contact, for she could not be induced to cooperate in the examination. The temperature was 104.8 F.; the pulse rate, 178; respiration rate, 40, and the blood pressure 100 systolic and 60 diastolic. The nonprotein nitrogen of the serum measured 76 mg. per hundred cubic centimeters; chlorides, 95.1 milliequivalents, and the carbon dioxide-combining power, 14.1 milliequivalents. The spinal fluid was normal. An abscess was developing in the right breast. No neurologic abnormalities were noted.

During the next few days the temperature and the pulse and respiration rates decreased to normal levels, and the chemical constituents of the blood also reached normal values. The neurologic condition, however, was slow to improve.

On the fifteenth day post partum, she was confused and could not understand what was said to her or form any words. She could not swallow and had to be tube fed. All four extremities were weak. There was only moderate weakness of movement at the shoulder and elbow joints, but there were complete loss of tone and almost complete paralysis of all muscles which acted at the wrist and the finger joints. The right arm was more severely affected than the left. The legs were affected in a fashion similar to that of the arms, but the flaccidity at the ankle joints was not so severe as that at the wrist joints. The tendon reflexes were brisk, and ankle clonus and extensor response were elicited on plantar stimulation. The Hoffmann digital reflex was present. She was, of course, incontinent.

On the eighteenth day the abscess of the breast was incised and drained. There was no particular change in her neurologic condition, but she seemed to be in somewhat better contact, though rather negativistic.

Six weeks after delivery, she seemed to understand what was happening around her. She tried to talk but could not form words. She had regained some power of movement in the distal parts of the extremities. She could sit up in bed for a time. There was still incontinence. Biopsy showed perivascular infiltrations and hyalinization of muscle fibers.

At the end of the second month she could form a few words indistinctly and could walk a short distance. There was severe ataxia of all extremities of cerebellar type. Her mental condition was profoundly deteriorated. She was discharged from the hospital.

When seen one year later she was pregnant again, being in the last trimester. Almost all the neurologic signs had disappeared. There was a mild sensory speech aphasia. Motor power was good, but difficulty in writing, due to ataxia, persisted. Light touch and pain stimuli were still not as well appreciated in the right forearm, hand, lower leg and foot as in the left. All the tendon reflexes were hypoactive. The Hoffmann responses remained. In all, there had been a remarkable recovery during the year's interval.

Comment.—Since these women were both young and in early puerperium and, moreover, had been given moderate doses of a relatively nontoxic sulfonamide, i. e., sulfathiazole, the possibility is suggested that the pregnancy may have rendered them especially sensitive to the drug. Among many thousands of nonpregnant patients treated for a much longer period and with larger doses, I have observed no similar

reactions. One might be inclined to assume that the first administration of the drug had caused sensitization, since the second administration was followed by such a violent reaction. The neurologic picture was characterized by prolonged stupor and confusion, loss of speech and inability to swallow, and the residue included profound cerebellar ataxia and pronounced reduction of mentality.

Long and Bliss [69] stated that polyneuritis is not uncommon when sulfanilyl dimethyl sulfanilamide or sulfanilyl sulfanilamide is used and that it is rare with other derivatives. Blankenhorn,[70] however, estimated that it may occur in 1 per cent of patients treated with sulfadiazine, sulfathiazole or sulfapyridine. He reported 6 cases, in only 1 of which there had been previous treatment with a drug of this type. No symptoms other than those of polyneuritis were noted. The blood levels were not excessive. In 5 cases more than 50 Gm. of the drug was administered. In some cases polyneuritis due to these drugs is exceptionally severe, and there may be little tendency toward improvement after a year.

DAMAGE TO THE NERVOUS SYSTEM DUE TO SPINAL ANESTHESIA

This condition is mentioned merely because it may occur in cases in which spinal or caudal anesthesia is induced during delivery, although it seems clear that it is not more apt to occur in such circumstances than at other times. It seems wise, however, to call attention to the possibility of this complication, since it should be considered in differential diagnosis of lesions of the spinal cord occurring during this period. A variety of clinical syndromes have been attributed to the use of anesthetics such as procaine or amylocaine hydrochloride (stovaine®) though it is not always clear that these substances are actually to blame. These conditions may be mentioned briefly.

Signs of damage to the spinal cord or the spinal nerve roots may appear immediately or a short time after the injection and subsequently persist or recede rapidly. In a few instances it has been shown that there was damage to the myelinated fibers lying in the periphery of the cord and the same condition may be produced in experimental animals by injection of large doses of local anesthetics. Apparently, these drugs have a lipolytic action.

The evidence of damage to the spinal cord or the spinal roots may appear days, or even weeks, after the anesthesia and may slowly progress to a fatal outcome months later. Such cases are very difficult to under-

69. Long, P., and Bliss, E.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939.

70. Blankenhorn, M. A.: Multiple Peripheral Neuritis Occurring in Sulfonamide Therapy, Ann. Int. Med. **20**:423, 1944.

stand. Permission for autopsy has been secured in a few cases, but merely marginal degeneration has been noted as in the first case described.

Adhesive arachnoiditis may follow the use of spinal anesthetics. There may be damage to the spinal cord as well. Manometric tests reveal obstruction of the spinal subarachnoid canal. In some cases of this type the symptoms may grow slowly worse, owing, no doubt, to constriction of the cord by the scar tissue.

There may be meningeal irritation immediately after the injection of the anesthetic, with or without cranial nerve palsies. The sixth cranial nerve is, perhaps, the most frequently affected. The process seems to be a chemical irritation, which clears up quickly.

True meningitis, due to bacteria, has also been described, especially when continuous caudal anesthesia is maintained during labor. Brown [71] discussed 10 cases of this type.

Hemiplegia, aphasia and other cerebral syndromes may occur during anesthesia, presumably due to pronounced fall of blood pressure and thrombosis of a cerebral artery. I have observed 2 cases of this type, in which persisting hemiplegia and aphasia resulted.

EFFECTS OF ABORTIFACIENTS

A number of drugs have been employed to produce abortion, and all of these are capable of producing untoward effects. The list is a long one, and only a few will be mentioned here.

In certain European countries, especially Netherlands and Yugoslavia, apiol, a volatile oil derived from parsley, has been employed. This is often used in combination with oil of tansy and oil of savin. Both these drugs are poisonous, but it is believed that the apiol is responsible for the effects on the nervous system. Recent pharmacologic investigations have revealed that an impurity in the apiol, namely, triorthocresylphosphate acid ester, is to blame. It will be recalled that this is the substance which was found to be responsible for the Jamaica ginger paralysis. After the ingestion of the drug, gastrointestinal symptoms appear, which may last two or three days. There is then a latent period, lasting, perhaps, two or three weeks. After this there develop weakness and numbness, and finally paralysis, of the extremities, the legs being affected more severely than the arms. There is little pain and usually no loss of sensibility. Soon atrophy occurs and may become very severe. After a few weeks the condition becomes stationary, but improvement does not begin, it is claimed, for six months. Eventually, almost complete recovery results, according to the European authors[72]. If this condition is really due to triorthocresylphosphate acid ester, how-

71. Brown, W. W.: Meningitis Following Continuous Caudal Anesthesia, Am. J. Obst. & Gynec. **53**:682, 1947.

72. Smith, S.: Forsensic Medicine, London, J. & A. Churchill, 1938.

ever, one would expect the polyneuritis to be followed by spastic paraplegia, for that is the common outcome in cases of Jamaica ginger paralysis in this country. Only 1 case of polyneuritis due to apiol has been reported from this country, that of Denison and Yaskin.[73]

Quinine is also a popular abortifacient. When a large dose is taken there may be transient deafness and loss of vision. Occasionally, optic nerve atrophy may result. This is characterized by extreme narrowing of the retinal arteries and high grade pallor, even when the reduction of vision is moderate, so that the ophthalmoscopic changes in the nerve head are severer than the loss of function. With very large doses, or in occasional cases of idiosyncrasy, there may be mental confusion, vomiting and convulsions. The heart action may be affected, and death may result from paralysis of respiration.

Ergot has been used for this purpose for many years. As a result of excessive doses, there may be vomiting, dizziness and circulatory changes in the extremities, which may result in gangrene. Twitchings of the muscles, and even convulsions, may occur. Bleeding from the mucous membranes has been described. Vision fails, and the pulse becomes rapid and weak. Death occurs in coma. Hydrastis has a similar effect.

Lead has been occasionally employed as an abortifacient, usually in the form of pills made from diachylon, or lead plaster. Vomiting, thirst, constipation, suppression of urine, headache, drowsiness and convulsions may result. Palsies of the peripheral nerves occur, and encephalopathy with optic neuritis and edema of the brain is seen.

CONDITIONS DUE TO VITAMIN DEFICIENCY

POLYNEURITIS ASSOCIATED WITH PERNICIOUS VOMITING

This condition has been known for many years, but it has been only in recent years that comprehensive studies have appeared and any understanding of its cause has been attained.

It is well known that morning nausea is present in the early months of pregnancy in about one half of all cases. In about 1 case in 150, according to Stander,[74] the vomiting is severe enough to require hospital treatment. In a very small percentage of such cases the vomiting increases in frequency and becomes uncontrollable, i. e., pernicious. This is most apt to occur in the first or second pregnancy. The patient becomes emaciated and dehydrated. In the third or fourth month of pregnancy some of these patients begin to exhibit weakness of the legs, which soon extends to the thighs and hips and later to the hands and

73. Denison, R., and Yaskin, J. C.: Apiol Polyneuritis, J. A. M. A. **104**:1812 (May 18) 1935.

74. Stander, H. J.: William's Obstetrics, ed. 8, New York, D. Appleton-Century Company, 1941.

arms. There are apt to be pains and paresthesias of the distal type, and actual loss of cutaneous sensibility is often found. In severe cases the muscles of respiration may be affected. Loss of control of the sphincters is sometimes mentioned. Optic neuritis or retrobulbar neuritis is seen in about 10 per cent of cases, and retinal hemorrhages may also occur. Mental changes are common. In general, these are such as are observed in intoxications and include delirium, confusion and disorientation.

In some cases, but not in all, there are generalized edema, tachycardia, enlargement of the heart and dyspnea.

Albuminuria may be present, and red cells may be found in the urine. There is, however, no evidence of renal failure or hypertension.

Berkwitz and Lufkin [75] made postmortem examinations in 3 cases and collected the reports of 6 more from the literature. Jones,[76] McGoogan [77] and Bingham [78] have made more recent studies, with the same results. There is always extensive degeneration of the peripheral nerves with degenerative changes in the motor cells of the spinal cord. In some instances petechial hemorrhages have been observed in the brain and spinal cord. These changes are stated to be identical with those described in beriberi. The kidneys and liver show merely cloudy swelling. According to Jones,[76] the changes in the heart muscle typical of beriberi have not been described in cases of pernicious vomiting. Stander [74] stated that there are central necroses of the liver and tubular degeneration in the kidneys, which suggest toxemia.

In the past, the polyneuritis of pregnancy was regarded as the result of toxemia, since the active stage of the disease ended with delivery or with the death of the patient. More recently, however, it has been attributed to a vitamin deficiency. Strauss and McDonald,[79] in 1933, and many others since then have claimed that the vomiting, the great demands of the fetus and the use of high carbohydrate diets to control the vomiting result in depletion of vitamin B, and polyneuritis is a result. The changes observed at autopsy are said to be identical with those of beriberi, and it is also claimed that large doses of thiamine and other elements of the vitamin B complex reduce the mortality in striking fashion and tend to bring about recovery. McGoogan [77] collected figures which support this view very strongly. He stated that for a series of 105

75. Berkwitz, N. J., and Lufkin, N. H.: Toxic Neuronitis of Pregnancy, Surg., Gynec. & Obst. **54**:743, 1932.

76. Jones, O. H.: Polyneuritis of Pregnancy, Am. J. Obst. & Gynec. **45**:869, 1943.

77. McGoogan, L. S.: Severe Polyneuritis Due to Vitamin B Deficiency in Pregnancy, Am. J. Obst. & Gynec. **43**:752, 1942.

78. Bingham, A. W.: Polyneuritis of Pregnancy, Am. J. Obst. & Gynec. **32**:144, 1936.

79. Strauss, M. B., and McDonald, W. S.: Polyneuritis of Pregnancy, J. A. M. A. **100**:1320 (April 29) 1933.

patients who did not receive vitamins the death rate was 32.2 per cent, whereas for a series of 40 patients who were given vitamins in one form or another the mortality was merely 7.5 per cent. It must be pointed out that the cases in which vitamins were given were the more recent ones, and that it is possible that the patients received better nursing care and more modern treatment in general. It must also be admitted that in certain instances, especially of the severer and more advanced disease, vitamins seem to be of no value. Various laboratory studies seem to show that these patients are actually depleted of vitamins and that their vitamin intake has been reduced. One has, therefore, strong evidence that the polyneuritis is due to vitamin deficiency, particularly deficiency of thiamine; but it is probably not justifiable to conclude that the case is fully proved. The cause of the vomiting is obscure, but it is probable that it is brought about as a result of a metabolic disorder associated with pregnancy.

The fetal death rate is high. Some babies die in utero, and spontaneous abortions are common. Viable infants are said to do well, however, in contrast to the babies of women in the East with beriberi, who are likely to die of beriberi or Wernicke's encephalopathy, especially if they are breast fed.

The mortality seems to be below 10 per cent if vitamins are used. According to all authorities, the paralyses are slow to disappear, although it is stated that in the end complete recovery is to be expected. Disturbances of vision, as a rule, are of brief duration. The cardiovascular symptoms do not last long after delivery.

Treatment should be begun early, as soon as the vomiting starts, and large doses of the vitamin B complex administered. Some authors advise the use of liver extract as well, and iron and hydrochloric acid may be administered to control the anemia which is often present.

It is uncertain whether abortion is of any value. Some authorities recommend that the uterus be emptied if the patient does not respond to conservative treatment. In some instances, the active symptoms disappear as soon as delivery is effected. In others, this procedure seems to be of no value and does not avert a fatal outcome.

A case history is given in which the use of vitamins in large doses from the onset of the vomiting until delivery did not check the progress of the polyneuritis.

Persistent vomiting throughout pregnancy. Despite use of vitamins. Development of severe polyneuritis with facial diplegia and, later, increased intracranial pressure. Beginning improvement two weeks after delivery, but progress very slow. Subtemporal decompression required to save vision.

H. B., a white woman aged 26, became pregnant in January 1942. She soon began to vomit, and, despite all treatment, the vomiting continued throughout the pregnancy. She was given excellent nursing care, and her nutrition was never seriously impaired. From the beginning it was feared that a vitamin deficiency

might develop, and she was given vitamin B complex and numerous other vitamins, in large doses continuously. These were given hypodermically as well as orally. Nevertheless, at the end of the fourth month, she noticed numbness developing in her hands and feet, and a severe polyneuritis gradually appeared. At term her symptoms were at their worst. She was nearly helpless and could not walk. The hands and wrists were very weak, so that she could not feed herself. There was no power at the ankle or knee joints. Bilateral facial paralysis, which had its onset at about the fifth month, had, however, disappeared. Delivery of twins was accomplished without difficulty, and about two weeks later it was evident that the patient was improving, though her progress was very slow.

A few weeks post partum she began to complain of headache and then of blurring of vision. Her physician discovered that she had bilateral papilledema.

On examination in January 1943, the patient was found to be well nourished and well developed. Her mental state was clear. The temperature was normal, but the pulse rate varied from 110 to 120. There was paralysis of all movements at the ankle and toe joints. Movements at the knee joints were very weak, and at the hips there was only a little weakness. The muscles of the arms were strong, but the intrinsic muscles of the hands were very weak. Scarcely any muscular wasting could be made out. The calves were somewhat tender, and there was some hypesthesia over the feet. The tendon reflexes were all absent, as were the plantar and abdominal reflexes. The cranial nerves were all normal except for the optic nerves. There was papilledema of 3 D. with marked engorgement of the veins but no hemorrhages or exudates. Vision was normal, and the visual fields were not reduced.

The spinal fluid pressure was 600 mm. of water. It contained 470 mg. of protein per hundred cubic centimeters. There were no cells. The Wassermann reaction of both the blood and the spinal fluid was negative. A ventriculogram revealed a symmetric system, of average size.

In view of the papilledema and the high spinal fluid pressure, it was decided that decompression must be performed to save vision. This was performed on January 15. The brain was normal in appearance but herniated strongly when the dura was incised.

Subsequently the papilledema receded and the headaches ceased. There was herniation of the brain for a number of weeks, however. The patient continued to make slow progress in regaining her strength, and when she last reported she was getting about fairly well.

BERIBERI AND WERNICKE'S ENCEPHALOPATHY

In Japan and in other parts of the Orient—in fact, in any country where beriberi is prevalent—it is known that pregnancy in women living on inadequate diets or women with mild symptoms of beriberi will often induce active and severe manifestations of this disease.[80] The mother may have merely the common sign of wet beriberi, or perhaps also an encephalopathy, i. e., Wernicke's hemorrhagic encephalopathy (acute hemorrhagic polioencephalitis). The baby seems to acquire Wernicke's encephalopathy, as a rule. Unless prompt and vigorous treatment with vitamin B complex is instituted, either or both the mother and the child are apt to die.

80. Hofman, J. A.: Beri Beri in Chinese Women and Its Relation to Childbearing, China M. J. **38**:987, 1924.

Beriberi seems to be merely a symmetric, peripheral neuritis, not unlike the common alcoholic polyneuritis. There are pain and tenderness in the extremities in most instances, though actual loss of cutaneous sensibility is not common. The distal muscles are weaker than the proximal ones, and the legs are affected, as a rule more severely than the arms. The tendon reflexes are lost. Optic neuritis may be associated. Loss of the voice and difficulty in swallowing are described. In the wet form of beriberi, the heart is dilated and feeble, and there is usually pronounced edema of the legs.

Wernicke's encephalopathy is manifest by cerebral symptoms, usually of abrupt onset. There are ptosis of the eyelids, nystagmus, diplopia and various ocular palsies. Ataxia and choreiform movements are frequently seen. The patient cannot stand, or even sit up. The mental condition progresses from restlessness and irritability to confusion, stupor and, finally, coma. Convulsions are common, especially in infants, and may lead to death in a few hours. General muscular rigidity with opisthotonos is described also in infants.

In both beriberi and Wernicke's encephalopathy, there are almost without exception both vomiting and diarrhea, so that four types of symptoms characteristic of vitamin B deficiency are present—gastrointestinal, polyneuritic, cardiac and cerebral.[81]

The pathologic changes are well known. In beriberi there is degeneration of the peripheral nerves, and in the encephalopathy multiple petechial hemorrhages occur in the periaqueductal gray matter and around the walls of the third and fourth ventricles.

It is claimed that the prompt administration of thiamine hydrochloride in adequate doses is followed almost at once by striking improvement in the patient's condition and, if the illness has not progressed too far, by rapid recovery. The so-called dry beriberi, which is a chronic condition, is not so easily controlled, it is said.

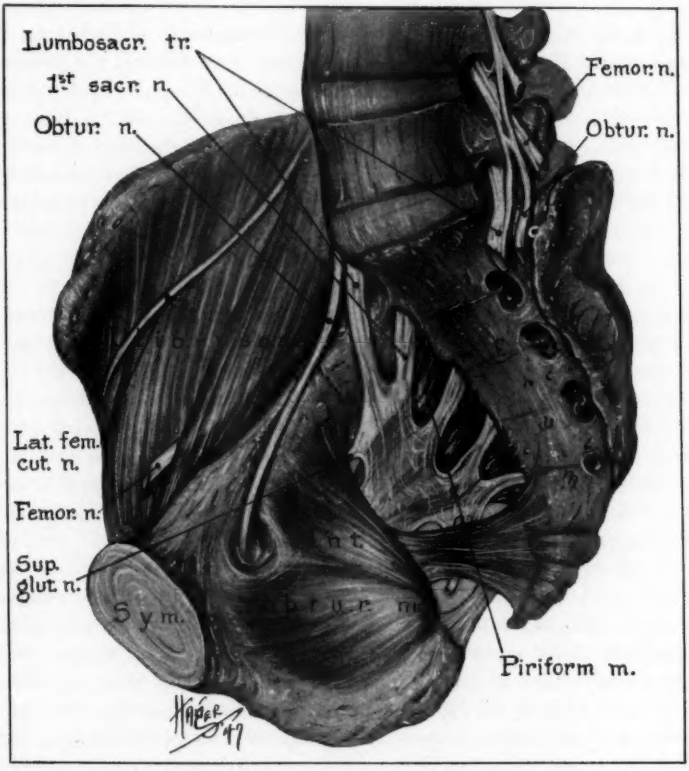
CONDITIONS DUE TO TRAUMA

MATERNAL LUMBOSACRAL PLEXUS PARALYSES DURING DELIVERY

It has been known for many years that parturition may cause injury to the lumbosacral nerves, and a number of papers have been devoted to this problem. There is no reason to doubt that these palsies are simple and the direct result of compression of the nerve trunks in the pelvis, either by the baby's head or by obstetric forceps, though certain authors have questioned this belief. In almost all cases the labor has been prolonged and delivery difficult. In my experience, a large baby has seemed

81. Denny-Brown, D.: Neurological Conditions Resulting from Prolonged and Severe Dietary Restriction, Medicine **26**:41, 1947. de Wardener, H. E., and Lennox, B.: Cerebral Beri Beri (Wernicke's Encephalopathy), Lancet **1**:11, 1947.

to be the commonest cause of this unfortunate complication, but a contracted pelvis is also frequently to blame. An obliquely contracted pelvis is apt to lead to damage of the nerves lying in the shorter diameter. This condition may lead to recurrence of symptoms with each delivery. I have seen such a recurrence in one unfortunate woman four times. It is possible that general anesthesia may play a part in making the



Anatomic relations of the lumbosacral nerve roots.

nerves more sensitive to pressure, but I have found no clear evidence to prove this supposition.

The anatomy of the pelvis and the position of the lumbosacral nerve roots make the clinical manifestations clear. The lumbosacral portion of the cord, which includes the fifth lumbar root and a component from the fourth lumbar root as well, passes downward over the bony brim of the true pelvis and is at this point especially vulnerable to pressure (figure). The obturator and superior gluteal nerves lie just anterior

to the lumbosacral part of the cord and are also exposed to compression, as is the first sacral root, which lies just posterior to the lumbosacral portion of the cord. The lower sacral nerve roots, however, are cushioned by the pyriformis muscle, and the femoral and lateral femoral cutaneous nerves are placed more laterally and above the superior strait of the pelvis, where they are in less danger.

The lumbosacral portion of the cord contributes a part of the motor nerve supply to the tibial and peroneal muscles, the extensor digitorum longus, the flexor digitorum longus, the extensor hallucis longus and some of the intrinsic muscles of the foot. The sensory field extends over the outer aspect of the foot and ankle, corresponding in location and extent very closely to that of the common peroneal nerve. The first sacral root supplies a part of the innervation of the tibialis posterior, the peronei, the extensor digitorum longus, the flexor digitorum longus, the flexor hallucis longus, the extensor hallucis longus, the soleus, the gastrocnemius, the hamstrings, the pyriformis, the obturator internus abdominis, the gemelli, the gluteus maximus and the intrinsic muscles of the foot. Its sensory field includes the toes and the sole. The obturator nerve supplies the adductors of the thigh, the obturator externus abdominis and the gracilis. The adductor longus may derive an accessory innervation from the femoral nerve. The sensory field of this nerve is a small area of variable extent lying on the inner aspect of the thigh, between the knee and the groin. The superior gluteal nerve supplies the gluteus medius and the gluteus minimus, as well as the tensor fasciae latae. It must be kept in mind that there is some variation in the distribution of the motor nerve roots and that exceptions to these statements are not uncommonly encountered.

With this brief review of the anatomy, the clinical picture may now be discussed. Toward the end of pregnancy the patient may complain of pains radiating into one or both legs, but as a rule there are no indications of the impending disaster until delivery, which, as has already been stated, is almost always a difficult one. There is then severe pain in one or both legs, associated with numbness and weakness. The pains rarely last more than a short time, but the loss of function is more persistent. The signs and symptoms most frequently encountered are those referable to injury to the lumbosacral portion of the cord, and may be easily mistaken for those due to injury of the common peroneal nerve. There are weakness of extension (dorsal movement) of the ankle with paralysis of the tibialis anterior in many instances and weakness of both flexion and extension of the toes. Inversion and eversion of the foot may be weak, but flexion (plantar movement) of the ankle is strong and the ankle jerk is preserved. Some degree of hypesthesia may be found over the outer aspect of the foot and ankle, which does not as a rule extend onto the sole and which is best made out with a pin.

The first sacral root is not often affected alone, being usually involved in addition to the lumbosacral region of the cord. In the case of such combined lesions, one finds paralysis of extension (dorsal movement) of the ankle, weakness of flexion of the ankle, complete or almost complete loss of inversion and eversion of the foot, great weakness of toe movements and some weakness of the hamstrings and the gluteus maximus. The sensory loss may extend over the dorsum and sole, as well as over the outer aspect of the ankle. The ankle jerk is usually lost or reduced. Involvement of the superior gluteal nerve causes both paralysis of abduction and weakness of internal rotation of the hip. When the obturator nerve is affected, one finds weakness, but as a rule not paralysis, of adduction of the thigh and perhaps some weakness of internal rotation of the leg and of external rotation of the thigh, due to lack of action of the gracilis and the obturator externus abdominis muscle, respectively. There may be a small area of hypesthesia on the inner aspect of the thigh.

My own experience may be given briefly. My colleagues and I have seen more than 20 cases in which this diagnosis was made or suspected strongly. In some of these cases it was impossible to obtain a reliable history. In 10 of the cases some form of dystocia was present. In 6 cases the baby was very large, weighing 5,000 Gm. or more, and in 5 cases the pelvis was contracted. The lumbosacral portion of the cord was involved in 8 cases, and in 3 of these the condition was bilateral. In 4 instances the first sacral root was also affected. In 3 cases the obturator nerve was affected, and in 1 of these the paralysis was bilateral. The superior gluteal nerve was involved in 3 cases. We have never seen complete recovery from this condition when outspoken physical signs were discovered on examination. In 5 cases of this series there was moderate improvement in from three months to one year. In 4 cases there was very little improvement in eighteen months to six years. In 1 instance there was pronounced improvement in three months, but severe disability was still present. As a rule, there is limited improvement in the first few weeks after delivery, which probably represents return of function in nerve fibers which have suffered only reversible changes. Thereafter, there is only slow and limited improvement. The commonest residuum is weakness of extension (dorsal movement) of the ankle. Pain has never persisted more than a short time.

The diagnosis is based on the clinical features outlined. The chief problem is the differentiation of this condition from extrusion of an intervertebral disk in the lumbar region and from pressure paralyses of the peripheral nerves due to injury sustained during anesthesia. The differential diagnosis is discussed in connection with the description or extrusion of intervertebral disks.

A Negro woman aged 33, with generally contracted pelvis. Paralyses of both obturator nerves after difficult delivery, with involvement of the lumbosacral portion of cord, first sacral root and superior gluteal nerve on the right side. Only moderate improvement nine months later.

B. C., a Negro woman aged 33, gave birth to an infant on Aug. 12, 1946. She had a generally contracted pelvis, and labor lasted twenty-two hours. After she had been in labor for some time, it was attempted to apply forceps, without success. Finally she was brought to the hospital, and eventually birth occurred spontaneously. During delivery she complained bitterly of pains in her legs, and on the following day she noted weakness and numbness in her legs, in addition to the pains.

Examination on August 17 revealed weakness of the adductors of both thighs, amounting nearly to a paralysis on the right. In addition, extension and abduction of the right thigh were nearly lost. Flexion was weak at the right knee. At the right ankle, both flexion and extension were lost, or nearly lost, and (dorsal) extension was much reduced on the left. The right ankle jerk was lost, and the left was present. The knee jerks were, of course, intact. There was hypesthesia over the outer aspect of the right foot and ankle; a slight sensory change was present over the inner aspect of each thigh but could not be outlined properly. For several days the patient complained of severe pain.

Owing to a difference of opinion about the diagnosis, a spinal puncture was performed and iodized oil U. S. P. injected. Roentgenograms of the spine were also taken. None of these tests revealed any abnormality.

On reexamination on September 3, some strength had returned in the left adductors and the sensory loss covered a much smaller area, but there was little change otherwise and the patient walked with much difficulty. Her back was flexible.

On June 26, 1947 the patient was reexamined. There was still pronounced weakness of extension, abduction and adduction of the thigh, and the buttock was somewhat wasted. Some return of power, however, was noted. There was still weakness of the adductors on the left. At the right knee there was still weakness of the hamstrings, which were a bit wasted. At the right ankle dorsiflexion was nearly lost and plantar movement was also weak. The calf was conspicuously wasted and the ankle jerk absent. In general, it may be said that after nine months there had been very moderate improvement and that all the physical signs found on the first examination were still evident, though not quite so pronounced.

PRESSURE PARALYSIS OF PERIPHERAL NERVES FROM INJURY RECEIVED DURING ANESTHESIA

Little has been written about pressure paralyses of peripheral nerves from injury received during anesthesia, but I have seen a number of them. They are observed, as a rule, only in patients who have been under anesthesia more than a short time, especially those who have been delivered by cesarean section. They may result, however, from very brief anesthesia. I have observed a number which developed when thiopental sodium was employed. Circulatory collapse also seems to favor this development. Certain factors which play an important role in the production of pressure paralyses in nonpregnant women must also be mentioned. Alcoholic, and diabetic patients and persons receiving arsenical drugs or bismuth are especially susceptible to this condition. No doubt, the same statement might be made of persons suffering from vitamin deficiency, though this has not been evident in our experience.

The radial nerve is most often affected, and the common peroneal nerve is probably next in order of frequency. The ulnar nerve is not uncommonly involved, but it is rare for the median nerve to be injured. The roots of the brachial plexus may be affected, especially the fifth and sixth roots, though occasionally the lower roots, or even all the roots, are involved. It is of interest that one may encounter complete loss of motor power without any corresponding sensory loss. Denny-Brown and Brenner [82] have reproduced this condition in experimental animals.

In most cases the mechanism seems to be direct pressure on the nerve trunk at a point where it lies over a bony prominence. No doubt the relation of the common peroneal nerve to the head of the fibula and the exposed position of the ulnar nerve at the elbow are responsible for the frequency with which these nerves are involved. The straps of the stirrups used for the lithotomy position are a frequent cause of peroneal nerve paralysis in women post partum. The nerve is compressed on the anterior aspect of the leg in the region of the knee. Injury to the nerve may be partial, producing numbness and weakness of eversion of the foot, or there may be complete foot drop. The radial nerve may be affected either above or below the elbow and is probably compressed against the outer aspect of the humerus or against the radius. It is also directly injured by subcutaneous injections of morphine and other substances. Some of the brachial plexus paralyses seem to be due to pressure in the supraclavicular fossa, and others, to pressure in the axilla. They are usually unilateral but may be bilateral. Occasionally one sees a patient whose condition was precarious during operation and whose blood pressure was taken at frequent intervals, with the result that all the nerves of the arm were paralyzed by the pressure of the cuff. In several cases I have observed that the brachial plexus was injured by stretching. During the operation the arm was strongly abducted and elevated to facilitate transfusion. The result was rather characteristic, for scattered paralyses were found which indicated involvement of the upper and lower roots and could not be easily explained by any local pressure.

Paralysis of the femoral nerve following delivery with the use of anesthesia has been described several times. It has been attributed to strong flexion of the thighs on the abdomen with abduction and outward rotation. This position is assumed to cause pressure on the nerve by Poupart's ligament or by the iliopsoas muscle.

The prognosis is always good in such cases. If the damage is not severe enough to cause actual degeneration of the nerve fibers, complete

82. Denny-Brown, D., and Brenner, C.: Lesions in Peripheral Nerves Resulting from Compression by a Spring Clip, Arch. Neurol. & Psychiat. **52**:1 (Jan.) 1944.

recovery can be expected in a matter of weeks. This is the usual outcome. Less commonly, there is actual degeneration of the nerve fibers, and recovery is delayed until regeneration can occur. In such instances recovery may be somewhat less than complete. However, I have never been able to follow the course of such a paralysis in which substantial recovery did not eventually occur.

As a rule, no treatment is required, for recovery is spontaneous. There is rarely any tendency to contractures or deformities. However, the patient usually wishes treatment of some type, and it is often desirable to employ massage, and perhaps splints. Thiamine hydrochloride may be given, for it seems to be harmless.

EXTRUSION OF INTERVERTEBRAL DISK DURING PREGNANCY OR DELIVERY

O'Connell [83] stated the belief that extrusion of a lumbar intervertebral disk is not an unusual event in pregnancy. He stated that in a series of 120 cases in which the diagnosis was verified at operation 39 were of females. Of these 39 female patients, 9 had borne children, and in 7 of the latter the symptoms began during pregnancy or the puerperium. He gave 4 case histories, with the operative findings and the end result, which was satisfactory in each instance.

O'Connell stated that it is possible that the tendency to relaxation of the pelvic joints which occurs during pregnancy may be paralleled by a similar change in the spinal joints and may favor extrusion of the intervertebral disks. He also mentioned the possible role of the increased lumbar lordosis and alteration of posture which are observed during pregnancy.

This author suggested that a percentage, perhaps a large percentage, of the maternal lumbosacral plexus paralyses attributed to compression of the spinal nerve roots in the pelvis during delivery are, in reality, due to extrusion of lumbar intervertebral disks. In my opinion, it is not difficult as a rule to distinguish these two conditions. I am convinced that both occur in pregnancy. In my experience, herniation of a lumbar intervertebral disk is a rare event in pregnancy, for in a series of 1,800 cases my colleagues and I have elicited the history of an onset during pregnancy very few times.

So much has been written about extrusion of the lumbar disks that it scarcely seems necessary to describe the symptoms in detail. Almost invariably it is one of the last three lumbar intervertebral disks which herniates and the third, fourth and fifth lumbar nerve roots and the

83. O'Connell, J. E. A.: Maternal Obstetrical Paralysis, Surg., Gynec. & Obst. **79**:374, 1944.

first sacral nerve root which are involved. As a rule, only one root is affected, though two or more may be involved, and in some cases complete extrusion of the disk into the spinal canal results in compression of the whole cauda equina. The process, whether it be due to compression or to stretching, is evidently more irritative than destructive, for the chief complaint in almost all cases is pain. This pain is typically located in the lumbosacral region, and in the leg in an area corresponding to the affected dermatome or dermatomes. It is increased by movements of the spine and by coughing, sneezing and straining. There is also almost invariably spasm of the lumbar muscles, resulting in reduction of the lumbar lordosis, in limitation of movement and often in tilting of the pelvis with lateral curvature of the spine. The straight leg–raising test gives a positive reaction.

In 50 per cent of cases, or perhaps more, there is evidence of loss of conduction in the affected nerve roots. Numbness over the affected dermatone, usually the outer aspect of the foot, ankle and calf, is often noticed and may be associated with mild hypesthesia. The calf muscles may be slightly weak and display moderate wasting, which is due partly to disuse and partly to reduction of the motor innervation. The ankle jerk is frequently reduced, or even lost. These statements apply, of course, to cases in which the fourth or fifth disk is extruded. When the third lumbar disk is herniated, the third, and sometimes the fourth, root may be involved, and, as a result, there may be weakness of the quadriceps muscle, loss of the knee jerk and sensory loss over the anterior aspect of the thigh.

The differences between the changes due to extrusion of lumbar disks and the lumbosacral plexus pressure paralyses should now be evident. Extrusion of an intervertebral disk may occur at any time during pregnancy or the puerperium, but rarely takes place exactly at the time of delivery, when the lumbosacral plexus pressure paralyses invariably appear. There is a striking tendency for repeated attacks of pain to occur regardless of pregnancy, and for each to be followed by a more or less complete remission. Pain is the presenting symptom, and as a rule there is very little loss of function. For example, foot drop is rare, whereas in lumbosacral plexus pressure paralyses it is the commonest finding. Pain in the back with limitation of movement and muscular spasm is, moreover, found only with herniation of the lumbar disks. Extrusion of the lumbar disks does not cause selective paralyses of the obturator or superior gluteal nerve, as pressure within the pelvis may. On the other hand, weakness of the quadriceps muscle, as O'Connell pointed out, is suggestive of herniated disk.

No doubt, the cervical intervertebral disks may herniate in pregnancy and cause compression of the roots of the brachial plexus or of the spinal cord. I have not observed such cases, however.

The pressure paralyses which may occur during delivery with anesthesia are, as a rule, not difficult to recognize and to distinguish from the conditions discussed in the previous paragraph. In such cases, one is dealing with lesions of peripheral nerves or lesions of the brachial plexus, for the lumbosacral plexus is protected from external pressure. These lesions are painless, though some patients confuse paresthesias with pain. The back is not affected in any way. Moreover, there is almost invariably prompt and substantial recovery, which is, as a rule, evident in a few weeks.

Another common condition which may cause confusion in differential diagnosis, namely, relaxation of the pelvic joints during pregnancy, should be mentioned at this point.[2] This process may give rise to symptoms as early as the second trimester or as late as the puerperium. It is manifest by pain in the lumbar region and thighs and by a wobbling gait. In a few instances, the patient cannot walk or stand because of the pain and prefers to lie in bed with the legs abducted. On examination, there is tenderness over the symphysis pubis and the sacroiliac joints, and movement may be demonstrated at the pelvic joints. The lumbar muscles and the adductors of the thighs may be tender, and muscle spasm may be present. Roentgenographic study reveals widening of the joints, but the clinical picture may not correlate with the roentgenologic picture. There may be pronounced pain and disturbance of gait with only mild separation of the joint and vice versa. If exposures are made with the patient standing on one foot and then on the other, striking movement of the bones may be evident. This condition attains its greatest severity at about the thirty-sixth week of pregnancy and tends to end in recovery as a result of fibrous union in the first six months after delivery.

NEOPLASMS

CHORIONIC CARCINOMA

This is a highly malignant growth that arises from the chorionic villi. It occurs, with rare exceptions, after pregnancy. A few instances have been reported in which such a growth arose in a teratomatous tumor situated in the ovary, the testis or even, in 1 instance, in the brain.[84]

The incidence is not clear, but the tumor [85] is rare. It has been stated repeatedly that chorionic carcinoma often follows the passage of a hydatidiform mole or an abortion, but rarely a term pregnancy.

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84. Stowell, R. E.; Sachs, E., and Russell, W. O.: Primary Intracranial Chorion-Epithelioma with Metastases to the Lungs, Am. J. Path. **21**:787, 1945.

85. Brews, A.: Hydatidiform Mole and Chorion-Epithelioma, J. Obst. & Gynaec. Brit. Emp. **46**:813, 1939. Mathieu, A.: Hydatidiform Mole and Chorion-Epithelioma, Internat. Abstr. Surg. **68**:52, 1939, in Surg., Gynec. & Obst., Jan., Feb. 1939.

Usually the first clinical symptom is vaginal bleeding, which occurs some time after the passage of a mole or after a normal delivery. This is probably a result of erosion of a vessel by the trophoblasts. Later there are abdominal pain, low grade fever, anemia and cachexia. The metastases are blood borne, and those to the lungs appear early. In fact, pulmonary symptoms may constitute the first evidence of the growth. Dockerty and Craig [86] reported a case in which deposits in the brain were the first symptom and the clinical picture was that of a primary tumor of the brain. The young woman had had the uterus removed four years previously because of a hydatidiform mole. It is of interest that this tumor may lie dormant for long periods, though it is usually evident within six months after delivery.

The diagnosis may be established by the histologic study of material expelled from the uterus spontaneously or removed by curettement. However, metastases may be already widespread, and curettements may show nothing. Biopsy of tumors appearing on the labia or elsewhere has led to the proper diagnosis. Recently the Aschheim-Zondek or the Friedman test has been helpful. In normal pregnancies, the titer of chorionic gonadotropin falls to a low level shortly after delivery. In cases in which a chorionic carcinoma is present, however, the titer rises to high levels after delivery. Every woman who has vaginal bleeding in the postpartum period should have such a test. If the symptoms of a brain tumor appear in a woman of the childbearing age, a careful obstetric history should be taken. If there is a history of a recent pregnancy, or passage of a mole, evidences of a chorionic carcinoma should be sought for before operation is undertaken.

Treatment once the tumor has been diagnosed is difficult. Immediate hysterectomy should be performed, and roentgenotherapy should be employed as well. It has been claimed that metastases may disappear after the primary growth has been removed, although this is open to question. Whether a cranial operation for metastases should be performed is debatable. The tumor carries such a high mortality rate that I feel that operation is contraindicated unless there is doubt concerning the nature of the intracranial mass.

EFFECT OF PREGNANCY ON NEOPLASMS AND ANGIOMAS

It is well known that cancer of the breast which develops during pregnancy displays a striking acceleration of growth, and there is reason to believe that other malignant growths may display a similar influence. Gliomas of the brain may seem to grow with special rapidity during pregnancy, but their behavior is so variable in any circumstances that it is impossible either to affirm or to deny that they are influenced by the state of pregnancy.

86. Dockerty, M. B., and Craig, W. McK.: Chorion-Epithelioma, Am. J. Obst. & Gynec. **44**:497, 1942.

The effect of pregnancy on angiomas and on certain slow-growing tumors, such as meningiomas and neurinomas, is sometimes very evident, however.

Cushing [87] reported the case of a woman with acoustic neurinoma in which symptoms appeared during pregnancy and then vanished, only to flare up during a second pregnancy in such a severe form that operation was required.

Hagedoorn [88] described a similar case. Bitemporal defects of the visual fields developed during pregnancy, associated with pallor of the disks. Vision cleared after delivery, but during the next pregnancy the field defects returned. This time they merely diminished after delivery but did not disappear. At a later date she again showed progressive loss of vision, though she was not gravid, and operation disclosed a parasellar meningioma.

Walsh [89] observed a woman aged 38 who had a central scotoma in the last trimester of pregnancy. This disappeared shortly after delivery but returned two years later. It was not until five years after the pregnancy that bitemporal field defects were found and operation seemed justified. A meningioma was removed from the olivary eminence.

The effects of pregnancy on angiomas are even more striking in some instances. I observed a young woman who displayed a large port wine stain on her forehead. At the age of 25, when she was six months' pregnant, left hemiplegia suddenly developed and she became unconscious. The hemiplegia receded, but she was thereafter subject to convulsions. At the age of 28 she came to the hospital. Except for the large angioma in the frontal region and a small one on the left thigh, clinical examination revealed nothing remarkable. A ventriculogram revealed a large cyst in the right frontal lobe, which communicated with the ventricular system. At operation the cyst was found to be lined with glial scar tissue, and there was a large arteriovenous angioma at its base.

Balado and Morea [90] described the case of a woman aged 36 who became incontinent during each of her first four pregnancies with recovery in the intervals. During the fifth pregnancy paralysis of the right leg developed, but there was no incontinence. The sixth pregnancy was uneventful, but during the seventh paraplegia developed, just eight days before delivery, and persisted for five months. At the fourth month of the eighth pregnancy she became completely paraplegic and died. Post-

87. Cushing, H.: Tumors of the Nervus Acusticus and the Syndrome of the Cerebellopontine Angle, Philadelphia, W. B. Saunders Company, 1917, p. 148.

88. Hagedoorn, A. L.: The Chiasmal Syndrome and Retrobulbar Neuritis in Pregnancy, Am. J. Ophth. **20**:690, 1937.

89. Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins, 1947.

90. Balado, M., and Morea, R.: Hemangioma extramedullar produciéndo paraplejias durante el embarazo, Arch. argent. de neurol. **1**:345, 1928.

mortem examination disclosed an extensive angioma enveloping the dura from the second to the seventh thoracic segment.

Delmas-Marsalet [91] described a similar case. A woman aged 18 had onset of pains in the arms and neck in the second month of pregnancy. These disappeared after delivery. During her second pregnancy the pains returned, and with them she noticed weakness of the legs. Again, the symptoms disappeared, though she thought there was some stiffness of the legs afterward. Three years later, though she was not pregnant, the pains recurred, and spastic paraplegia developed, with a sensory level at the second thoracic dermatome. Operation disclosed an angioma involving the cord from the second to the sixth thoracic segment.

It seems clear that the size of meningiomas and neurinomas is increased during pregnancy. It is probable that this is due to engorgement of the blood vessels and that the usual rate of growth is not materially increased.

The angiomas not only may become engorged but may be more likely to develop thromboses and hemorrhages during pregnancy. No doubt, in some cases the so-called myelitis of pregnancy is really due to an angioma aggravated by pregnancy.

CONDITIONS OF UNKNOWN ORIGIN

VISUAL FIELD DEFECTS SUPPOSEDLY DUE TO SWELLING OF THE HYPOPHYSIS DURING PREGNANCY

In 1923 Findlay [92] reported a series of cases of bitemporal hemianopsia occurring in gravid women. These field defects increased during pregnancy and then receded completely after delivery. In the same year, Carvill [93] announced the results of visual field studies in 88 women. She found bitemporal field changes in all but 5 cases. These defects disappeared by the time lactation ceased. In explanation of these observations, the work of Erdheim and Sturme on the changes in the pituitary gland during pregnancy was cited. These investigators had stated that the weight of the hypophysis in the normal woman averages 0.618 Gm., with a maximum weight of 0.750 Gm. A primipara near term has a gland averaging 0.847 Gm., with a maximum of 1.10 Gm.; multipara, a gland averaging 1.06 Gm., with a maximum of 1.65 Gm. It was assumed that the enlargement of the pituitary gland is responsible for compression of the optic chiasm, and hence for bitemporal field defects.

Since the publication of these reports, much has been written on the subject. Although several authors have confirmed these findings, an

91. Delmas-Marsalet, P.: Poussées évolutives gravidiques et image lipiodolée caractéristique des hémangiomes médullaires, Presse méd. **49**:964, 1941.

92. Findlay, C. E.: Bitemporal Contraction of Visual Fields in Pregnancy, Arch. Ophth. **52**:50, 1923.

93. Carvill, M.: Bitemporal Contraction of the Fields of Vision During Pregnancy, Am. J. Ophth. **6**:885, 1923.

equal number of reliable observers have not been able to detect any field changes, despite the use of excellent perimetric technic.

My colleagues and I have never encountered a patient in whom we were confident that the visual fields were altered as a result of pregnancy. Granted that the figures of Erdheim and Sturme are correct, the volume of the swelling seems hardly adequate to account for the field defects. Since the structures of the sella turcica are rigid, these would have to be ruptured to permit compression of the chiasm. Such rupture occurs in cases of pituitary tumor, but its direction is variable; as a result a great deal of variation is observed in the field defects. In no series of tumors of the pituitary gland have the visual fields been so uniformly constricted in both eyes as in the cases reported by Findlay [92] and Carvill.[93] We are inclined to suspect that the phenomenon is due to suggestion and to lack of attention on the part of the patient.

In another section, I shall discuss the rare instances in which pregnancy seems to cause swelling of a pituitary tumor with the production of true field defects, which may recede after delivery. This possibility should be kept in mind if temporal hemianopsia appears during pregnancy.

EFFECT OF PREGNANCY ON EPILEPSY

The influence of pregnancy on epilepsy is difficult to assess. There can be no doubt that young women who have never before had seizures may experience them during pregnancy, without any other evidence of toxemia or cerebral damage. In the majority of cases the seizures subsequently recur, as in cases unassociated with pregnancy. It is also well known that epileptic women may have more frequent and severer seizures during pregnancy than before, and in some instances at least the subsequent course of their disease is accelerated. However, it must be admitted that some epileptic women experience no increase of symptoms during their pregnancies, and may even seem to be improved. Wilson and Bruce [94] cited figures of Nerrlinger, who studied 157 pregnancies in 97 women. It was found that the seizures ceased in 28 per cent and increased in 35 per cent. A similar study by Burnett [95] gave essentially the same figures.

In the case of young women who first have convulsions during pregnancy and who continue to have seizures thereafter, one must consider three possibilities: (1) Pregnancy has brought latent epilepsy to light; (2) the patient has suffered cerebral damage during the pregnancy, and this is the cause of the epilepsy, or (3) the association is merely coincidental.

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94. Wilson, S. A. K., and Bruce, A. N.: Neurology, Baltimore, Williams & Wilkins Company, 1941, p. 1526.

95. Burnett, C. W. F.: A Survey of the Relation Between Epilepsy and Pregnancy, J. Obst. & Gynec. Brit. Emp. **53**:539, 1946.

Epilepsy is one of the commonest diseases which must be considered in the differential diagnosis of eclampsia. A proper and thorough history is of the greatest importance. It should be realized that patients and relatives will go to great lengths to conceal epilepsy, and it may be very difficult to elicit a history of convulsions or epileptic equivalents.

Ordinarily, the physical and neurologic examinations will fail to disclose any abnormalities unless there has been a preexisting cerebral injury that is the basis for the convulsions, such as an old head injury, vascular accident or neurosyphilis. The presence of hemiplegia, monoplegia, aphasia or increased or pathologic reflexes, however, should be carefully evaluated, since these conditions may be postepileptic phenomena, which may disappear within a few hours. The disease should be treated in the usual manner with anticonvulsant drugs. If status epilepticus is encountered, intravenous administration of barbiturates in large amounts, or even a general anesthetic, may be required. This is a dangerous complication when it occurs near term, and death may result from exhaustion.

Epilepsy does not affect the offspring directly. The laws governing the inheritance of epilepsy are still only poorly understood, and advice to families regarding the possibility of transmission of the trait is often difficult to give. Pregnancy should be discouraged when there is a definite family history of epilepsy.

EFFECT OF PREGNANCY ON MULTIPLE SCLEROSIS

Various authorities have discussed this problem briefly. Thus, Kinnier Wilson [96] stated:

> Symptoms have been first observed after pregnancy or parturition but a causal nexus between the two seems difficult to establish. I have seen the condition of paraplegic women improve at these times and during the puerperium, yet recall a case where childbirth intensified the symptoms thrice in succession.

Gowers [97] stated:

> I have known it [disseminated sclerosis] to begin during pregnancy, remain stationary until the next pregnancy and then become progressive.

Walshe [98] said:

> Pregnancy is not invariably deleterious to the course of events.—Yet it must be admitted that the malady may first come to notice after a confinement or may take a fresh lease of activity in these circumstances.

My experience is consistent with these statements. I have observed cases in which pregnancy seemed to have no influence on the course

96. Wilson and Bruce.[94]

97. Gowers, W.: Diseases of the Nervous System, ed. 2, P. Blakiston's Son & Company, 1901, vol. 2, p. 545.

98. Walshe, F. M. R.: Diseases of the Nervous System, Baltimore, Williams & Wilkins Company, 1945, p. 188.

of the disease; yet in other cases it has seemd to cause definite activation of the process. A case of this type may be mentioned briefly.

A woman aged 37 had a spontaneous abortion in 1932. Almost immediately after this she noticed numbness in both hands and forearms, associated with clumsiness and weakness. These symptoms disappeared in a month. Two years later, when she was again about three months pregnant, she was put to bed to prevent another abortion. Her legs grew weak and numb, and her left arm was affected in the same way. She could not walk without help. After delivery, she slowly improved, and after several months seemed to have made a complete recovery. Examination in 1937 revealed no unequivocal signs of organic disease. In view of the history, she was advised that another pregnancy might be dangerous. She disregarded this advice, however, and eventually gave birth to a healthy child. Her condition grew rapidly worse during this pregnancy, and when examined several months after delivery she showed severe spastic paraplegia and marked cerebellar ataxia. Since then, her condition has gradually declined, and she is now helpless.

I am inclined to believe that many of the cases described as instances of "pregnancy myelitis" are merely instances of multiple sclerosis activated by pregnancy.

EFFECT OF PREGNANCY ON MYASTHENIA GRAVIS

It was stated by Viets and associates,[99] who have recently made a valuable study on the subject, that pregnancy almost always causes a change in the course of myasthenia gravis. This finding, they concluded, proves that the relation is not merely one of coincidence. Patients with myasthenia gravis may have both relapses and remissions. As a rule, relapse is most apt to occur in the first trimester, sometimes before the patient knows that she is pregnant. According to Viets, relapses are usually not severe in patients who are receiving proper medication with neostigmine. In the past, they have frequently proved fatal. Until recently, it was customary to perform abortion early in pregnancy, for it was believed that labor would prove an excessive drain on the patient's strength. Viets opposed this procedure and pointed out that the first trimester is the most dangerous time for abortion in the whole nine months. He claimed that proper rest and medication offer less risk. Remissions are likely to occur in the last two trimesters. They are often abrupt and so complete that the patient is relieved of all symptoms. In some instances remission has occurred early in pregnancy, however. Labor is usually uneventful, though during severe relapses it may be unduly prolonged. Neostigmine should be used at this time, and in adequate doses. Nursing seems to have no untoward effects, though statements have been made to the contrary. Remissions may persist after delivery, and, as a rule, they average three to five months in duration.

99. Viets, H. R.; Schwab, R. S., and Brazier, M. A. B.: Effect of Pregnancy on the Course of Myasthenia Gravis, J. A. M. A. **119**:236 (May 16) 1942.

The differential diagnosis rarely presents great difficulty. Hyperthyroidism, which may be associated with symptoms strongly suggestive of myasthenia gravis, or may even complicate myasthenia gravis, must be kept in mind.[100] In such cases, the elevation of the basal metabolic rate, the exophthalmos and the cholesterol level of the blood are of value. The reaction to neostigmine is also helpful in the differential diagnosis. One must also mention the obscure cases of exophthalmic ophthalmoplegia in which no clear evidence of thyroid disease can be found. In our experience, these patients do not show improvement with neostigmine.

SO-CALLED MYELITIS OF PREGNANCY

Von Hösslin [1] collected a number of cases in which myelitis had occurred during pregnancy or during the puerperium. He described four types: (1) myelitis associated with disease of the vertebrae, (2) myelitis following severe hemorrhage, (3) myelitis associated with infection and (4) myelitis of unexplained origin. Alpers and Palmer [2] discussed the problem and reported 3 cases of their own. They gave several reasons to show that the relation is not merely one of coincidence: (1) The onset may be acute during pregnancy or the puerperium; (2) myelitis may recur during subsequent pregnancies, and (3) myelitis may recede after delivery. Nevertheless, it must be pointed out that improvement does not always occur after delivery and that the disease may subsequently progress when the patient is not pregnant.

Autopsies have been performed in a few cases. Alpers and Palmer [2] gave brief summaries of 3 cases. In each case the lesions differed, and nothing characteristic was evident.

It is hard to accept the theory that a true myelitis of pregnancy or the puerperium exists. I favor the belief that the development of myelitis during pregnancy is due to coincidence. It is suspected that multiple sclerosis is responsible for many such cases.

PSYCHOSES ASSOCIATED WITH PREGNANCY

Stander [74] stated that in a series of 34,356 deliveries at the Lying-in Hospital in New York psychoses occurred in 0.12 per cent. This incidence is much less than has been estimated in the past. The symptoms are apt to develop at term or during the puerperium but may occur at any stage of pregnancy. They may recur in association with repeated pregnancies, each time clearing up weeks or months after delivery. It is customary to divide these psychoses into three types: (1) those due to puerperal infection, (2) those due to toxemia and (3) those with

100. Brain, W. R., and Turnbull, H. M.: Exophthalmic Ophthalmoplegia, Quart. J. Med. **7**:293, 1938. Cohen, S. J., and King, F. H.: Relation Between Myasthenia Gravis and Exophthalmic Goiter, Arch. Neurol. & Psychiat. **28**:1338 (Dec.) 1932.

preexisting causes. The last are, of course, true psychoses, developing in unstable persons either as a result of the psychologic stress of pregnancy and motherhood or as a mere coincidence.

There seems to be a tendency in recent years among psychiatrists to minimize the importance of infection and of toxemia and to place greater stress on the patient's personality and the situational factors operative at such a time. It has been stated that there is no true puerperal psychosis and that every reaction type known to clinical psychiatry may occur during the course of pregnancy and the puerperium. Jacobs [101] stated that the largest group is that of the manic-depressive type. Schizophrenia is less frequently seen, probably because, as Jacobs suggested, schizophrenic patients are less apt to marry and to have children.

No doubt, the view expressed here is quite correct. Puerperal psychoses are essentially the same as other psychoses which arise without connection with pregnancy. This does not mean, however, that severe and prolonged infections may not cause delirium, or that extensive organic changes in the brain due to eclampsia and other processes may not produce a great variety of mental disorders, including dementia and changes in personality.

So many conditions have been mentioned in this paper that it seems wise to offer a brief summary of the various causes to be considered when neurologic manifestations appear during pregnancy or the puerperium.

101. Jacobs, B.: Etiological Factors and Reaction Types in Psychoses Following Childbirth, J. Ment. Sc. **89**:242, 1943.

SUMMARY

TABLE 1.—*Causes of Coma and (or) Convulsions*

	Time During Pregnancy or Puerperium	Frequency
Hypertensive encephalopathy	Any time	Common
Eclampsia	Last trimester, during delivery or just after	Becoming rare
Epilepsy	Any time	Fairly common
Intracranial hemorrhage	Any time	Fairly common
Pyemia with meningitis, abscess, septic sinus thrombosis and embolism	With postpartum infection	Uncommon
Uremia	Any time	Rare
Thrombosis of the cortical veins	Few days after delivery	Unusual
Diabetic coma	Any time	Uncommon
Hypoglycemic coma (diabetic)	Any time	Uncommon
Embolism		
Bacteria	Any time	Unusual
Air	Delivery or just after	Rare
Amniotic fluid (?)	Delivery	Unknown
Tetany	During pregnancy and lactation	Rare
Encephalopathy due to:		
Arsphenamine	Within 72 hr. after injection	Rare
Anesthetics	During anesthesia	Rare
Sulfonamides	During administration	Rare
Abortifacients(?)	Shortly after administration	Rare
Hepatic disease	Near term	Rare
Necrosis of the anterior lobe of the pituitary	Just after delivery	Very rare
Epidemic encephalitis	Any time	Rare at present
Psychoses	Any time	Uncommon

TABLE 2.—*Causes of Hemiplegia and Other Focal Cerebral Syndromes*

	Time	Frequency
Intracranial hemorrhage and thrombosis due to:		
Hypertension	Any time	Fairly common
Eclampsia	Last trimester, delivery and just after	Rare
Embolism	Any time	Rare
Hypertensive encephalopathy (transient palsies)	When blood pressure is at its height	Common
Thrombosis of the venous sinuses and cortical veins	Just after delivery	Rare
Vascular lesions due to syphilis	Any time	Uncommon
Neoplasm	Any time	Rare
Abscess and septic sinus thrombosis	With postpartum infection	Rare

TABLE 3.—*Causes of Blindness or Amblyopia of One or Both Eyes*

	Time	Frequency
Eclampsia	Last trimester, delivery and just after	Common
Hypertensive encephalopathy	With height of hypertension	Common
Multiple sclerosis	Any time	Uncommon
Uremia	Any time	Unusual
General anesthesia, especially nitrous oxide	Any time	Rare
Pituitary tumors	During pregnancy	Rare
Abortifacients	Just after administration	Rare
Air embolism	Post partum 4th to 8th day	Rare
Syphilis	Any time	Rare

TABLE 4.—*Causes of Polyneuritis*

	Time	Frequency
Pernicious vomiting	Third or fourth month	Common
Beriberi	Any time	Rare in United States
Abortifacients	Two or 3 weeks after administration	Unusual
Infections including diphtheria(?)	Some weeks after onset of infection	Unusual

TABLE 5.—*Causes of Lesions of Peripheral Nerves or Spinal Nerve Roots*

	Time	Frequency
Pressure paralyses from injury during anesthesia	During anesthesia or a very short time	Common
Lumbosacral plexus paralyses	Evident after delivery	Unusual
Extrusion of a lumbar disk	At any time	Rare

TABLE 6.—*Causes of Spinal Lesions*

	Time	Frequency
Multiple sclerosis	Any time	Uncommon
Spinal anesthesia	At once or after several weeks	Rare
Syphilis	Any time	Rare
Venous thrombosis	A few days after delivery	Rare
Pyogenic myelitis	With postpartum infection	Rare
Neoplasm	Any time	Rare
Rupture of dissecting aneurysm	Any time, most frequent in last trimester	Rare
Pregnancy myelitis	?	?

TABLE 7.—*Causes of Chorea*

	Time	Frequency
Chorea gravidarum (rheumatic disease)	First or second trimester	Uncommon
Hysterical chorea	Any time	Uncommon
Hemiballismus due to vascular lesion in corpus Luysi		Rare

Tables have been arranged under the heading of a prominent sign or symptom. Diseases are then listed, together with the approximate time they may be seen during the pregnancy and their frequency. Since this paper has dealt only with three chief groups of conditions, namely (1) those which are a direct result of pregnancy or delivery, (2) those which result from some procedure required during the course of pregnancy or delivery and (3) those which may be activated or aggravated during pregnancy or delivery, the tables are incomplete. One should refer to the section of the paper concerned when assessing the condition of an individual patient.

Tables such as these should be used with care, since they deal in generalities. However, they may be of value in planning the steps by which one may gain additional information in formulating a differential diagnosis. As a final word of caution, it should be added that other neurologic conditions, entirely unrelated to the pregnancy, may appear in a gravid woman. These must be considered before a final diagnosis is reached.

Dr. Eleanor Delfs, of the department of obstetrics, Johns Hopkins Hospital, rendered invaluable assistance in the preparation of the section on "Hypertensive Vascular Disorders." The section entitled "Conditions Due to Trauma" is almost exclusively the work of Dr. Frank R. Ford, and the illustration is from Dr. Ford's personal collection.

Obituaries

BERNARD BROUWER, M.D.

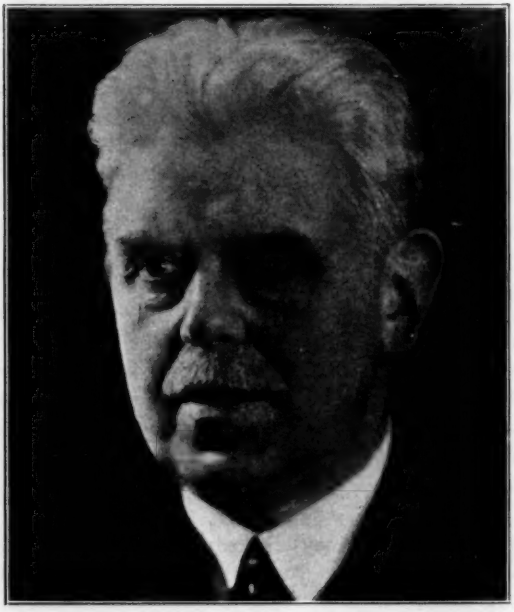
1881-1949

It is with a sad heart that I have learned of the death of Dr. Brouwer, a great loss to medicine, particularly to neurology, and, although I was associated with him for seventeen years, it will be difficult for me to express my admiration for the great work he achieved.

Professor Brouwer came to medicine at a period when neurology in Netherlands was at its peak. He was born in Amsterdam on March 23, 1881 and studied medicine at Amsterdam University, where he graduated in 1906. As a medical student I can still remember this blond giant—a giant both physically and mentally, who with an indomitable energy and enthusiasm began his scientific career in 1912 as assistant director of the Amsterdam Institute for Brain Research under Ariëns Kappers. He had also studied previously under Dr. Winkler, in Amsterdam, and Dr. von Monakow, in Zurich. Some time later Winkler went to Utrecht, in Netherlands, and left the chair of neurology at Amsterdam University to Dr. Wertheim Solomonson. Brouwer at that time, spent half of his time in Amsterdam at the Institute for Brain Research and at the same time developed his clinical experience in neurology as head of Wertheim Solomonson's outpatient clinic. From the beginning he voluntarily limited his private practice as a specialist in order to spend as much time as possible in the development of neurology.

In 1923 Wertheim Solomonson died suddenly and thereafter Brouwer was appointed professor of neurology at Amsterdam University. I had already worked with him as a medical student, and at that time he appointed me his first *chef de clinique,* so that I can probably be regarded as his oldest collaborator. We were located then at the fairly old-fashioned "Binnen-Gasthuis," which harbored at that time most departments of the University Hospital. Even then the name of the Netherlands school of neurology was such that many foreign postgraduate students came to Amsterdam and Utrecht, mostly to do research work. Among them were several American neurologists. Dr. Tracy J. Putnam was the best known of them during this period. Dr. Brouwer at that time started with Dr. Zeeman his fundamental studies on the optic pathways of monkeys after small lesions were produced in the retina. Dr. Putnam made an important contribution to this subject, which was published in a series of articles in the ARCHIVES.

In 1926 Dr. Brouwer was invited to give the Herter Lectures in the United States. He came back covered with honors and sadly aware how backward Europe was in neurosurgery. It became clear to him how necessary international cooperation is for the progress of medical science. After very difficult negotiations with the other faculty members (especially the surgeons) and the city administration controlling the University, Dr. Brouwer was finally given a new, modern clinic in the Wilhelmina Hospital in Amsterdam. He obtained (with the help of the Rockefeller Foundation and the city administration of Amsterdam) a



BERNARD BROUWER, M.D.
1881-1949

grant to send a surgeon who had also had neurologic training to the United States in order to study modern neurosurgery with Dr. Harvey Cushing, in Boston, and part of the time with Dr. Dandy, in Baltimore.

In the meantime he worked at the organization of his new 250 bed clinic. He planned it in such a way that the neurosurgeons worked under the neurologists. The clinic was organized in such a way that the patients were first seen in the neurologic section, and after this they were independently examined by the neurosurgeons. Operations were performed after mutual conferences about diagnosis and therapy. A

neurologist was always present at the operation and had the final say about the course of the operations. On the top floor of the building were, in addition to the surgical operating rooms, elaborate spaces for research. Dr. Brouwer conducted the neuropathologic work, while a Neurophysiology Institute, incorporated in the clinic, and the outpatient department were assigned to me.

Brouwer organized his clinic to perfection. Every detail was planned and supervised by himself, and he called his clinic his best scientific contribution to neurology. A very high medical authority in the United States, who had traveled all over the world and seen its medical institutions, told me unequivocally that he considered the Amsterdam Neurological Institute the best in the world. He stipulated that he did not make any exception to this.

More and more postgraduate workers from Netherlands and abroad came to work in the Institute; in this period Dr. Earl Walker, at present professor of neurosurgery at Johns Hopkins University, was one of its collaborators.

From Brouwer's more than 200 publications, I mention a small volume containing his Herter Lectures (Anatomical, Phylogenetical and Clinical Studies on the Central Nervous System. The Herter Lectures of the Johns Hopkins University, vol. 17, Baltimore, Williams & Wilkins Company, 1926). The three lectures were concerned with the following subjects:

1. The projection of the retina in the brain, after the widely known work with Zeeman, Putnam and others.

2. Pathology of sensibility. Here Brouwer developed his concepts of the older and newer central pathways in the spinal cord and the medulla oblongata. He distinguished paleosensibility, e. g., in the lateral column, and neosensibility, e. g., in the posterior column, according to the phylogenetic development. The neoformations are supposed to be the most vulnerable ones. Brouwer also emphasized that paleosensibility does not remain the same during evolution; the old parts develop further and are more finely organized in higher animals and in man, and therefore the differentiation between neosensibility and paleosensibility becomes vaguer. His final conclusion was that so-called vital sensibility is closely connected with autonomic functions and that much of it is brought to the central nervous system by nonmedullated fibers.

3. Significance of phylogenetic studies for the neurologist. He showed new and old elements in the inferior olivary nuclei and in the dentate nucleus, he described cases of neocerebellar atrophy (in the cerebellar hemispheres).

In 1940 World War II broke out. Brouwer was that year "Rector Magnificus" of the University of Amsterdam, a position comparable to dean of a college or university in this country; however, there each faculty member alternates in taking this place for one year. In 1946 I visited Netherlands, and Brouwer told me that his main purpose had been to continue working during the occupation at any price. This was mistaken by his fellow countrymen as collaboration, the more since the Germans appointed him Rector Magnificus for a second year, an irregular procedure. When the war was over, he was removed from his professorship in neurology by the Netherlands government. When I saw him last, he was already a sick man but was still visiting his beloved clinic. That year, Ariëns Kappers, the highly gifted director of the Amsterdam Institute for Brain Research, died, and Brouwer was appointed in his place. For about three years he showed again his power of organization of research work—like Samson in the Bible, who once more showed his original strength after his defeat. During that period he did important work on the hypothalamus and was invited to lecture in Zurich and in London and Manchester, England. His faithful wife, Helene Frommann, a pediatrician, was always at his side, organizing and smoothing out his life, so that he could devote himself to his work.

His scientific merits were honored in numerous ways; in 1920 the Ramaer Medal was awarded him for the best neuropsychiatric work over a five year period. In this country he was an honorary member of the American Neurological Association, the Neurological Society of New York, the Neurological Society of St. Louis and the Harvey Society of New York.

At the last International Neurological Congress, held in Paris in 1949, he was invited to speak in the name of all non-French neurologists. The same year he died suddenly, in the middle of his work, of a heart attack.

A really great figure, the dean of world neurology, has gone. It has been a great shock for all who knew him. It seems unbelievable that such indomitable strength and vigor could ever be broken. We who remain behind will remember him not only for his greatness but also for his kindness to every patient. He was a great organizer, a great scientist and, last but not least, a human being of warm feeling.

H. Holland de Jong, M.D., Los Angeles.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

A NEW NERVE BUNDLE OF THE HUMAN LUMBOSACRAL CORD. JULIO MARIA SOSA and WARREN ANDREW, J. Comp. Neurol. **87**:17 (Aug.) 1947.

Sosa and Andrew have continued the study of a superficial fasciculus of unmyelinated nerve fibers of the human spinal cord in abundant material. The fasciculus is demonstrated by silver methods as a thin band of transversely directed nerve fibers lying on the surface of the ventral white column beneath the pia mater. It is present both within the ventral median fissure and on the ventral surface of the cord. Within the ventral median fissure the fasciculus extends to the region of the ventral white commissure of the cord. Some of the fibers enter the commissure and after crossing the midline continue into the gray substance of the cord. The authors suggest that these fibers may originate from cells in the ventral gray column. The fasciculus leaves the ventral fissure to continue on the ventral surface of the cord as far as the region of the ventral motor root. Small nerve bundles of the fascicle are shown running transversely between the motor rootlets just before the latter emerge from the cord. The fascicle is in the lumbosacral region but is without an exact and constant topographic relation. Neither the origin nor the termination of the fibers is known. The fact that the fasciculus is unmyelinated and is not conspicuous except with silver stains may well explain why it has escaped notice until recently.

ADDISON, Philadelphia.

THE ROOTS OF THE FACIAL NERVE IN HUMAN EMBRYOS AND FETUSES. ANTHONY A. PEARSON, J. Comp. Neurol. **87**:139 (Oct.) 1947.

Pearson studied serial sections of human embryos and fetuses prepared with silver technics, such as pyridine-silver, strong silver protein (protargol) and a new silver-gelatin method. The lengths and estimated ages of the specimens from which the illustrations have been made are 45, 46 and 47 mm. (10 weeks); 65 mm. (11 weeks); 80 mm. (12 weeks), and 255 mm. (7 months). In addition, there are illustrations from the brain stem of an anencephalic newborn child, prepared by the pyridine-silver method.

When the cells of the geniculate ganglion separate from the embryonic acusticofacial ganglion, some remain within the internal auditory meatus in close relation to the vestibular ganglion and form an inner part of the ganglion of the seventh nerve. Pearson illustrates this condition in a 10 week old embryo. The fibers of the nervus intermedius are usually arranged in a number of smaller bundles, which enter the brain stem in separate fascicles. Within the brain stem the several components diverge in various directions. Some of the fibers end in the descending root of the fifth nerve. These are thought to be concerned with the conduction of stimuli arising from cutaneous receptors. This material throws no light on the question whether any of them mediate pain. The visceral afferent fibers enter the rostral portion of the fasciculus solitarius. The majority of these fibers turn caudad, but a few turn rostrad and constitute a prefacial portion of the fasciculus

solitarius. It is less conspicuous than the part of the fasciculus solitarius caudal to the entrance of the seventh nerve and is probably the site of the center for taste for the anterior two thirds of the tongue. The few proprioceptive fibers of the seventh nerve are thought to enter the caudal end of the mesencephalic tract of the fifth nerve. Other fibers of the nervus intermedius continue medial to the fasciculus solitarius and extend toward the midplane, becoming lost among the fibers which make up the genu of the seventh nerve. The sources of the general visceral motor fibers are still matters of speculation.

During the early migration of the neuroblasts of the seventh nerve to form the genu, there appears to be a migration of some of the neuroblasts across the midplane. This would account for a crossed component in the motor part of the seventh nerve. Pearson pictures these decussating fibers in the brain stems of the 65 and 255 mm. specimens and also in the brain stem of an anencephalic newborn infant. As a result of this crossing it is likely that the upper facial muscles receive an innervation from the motor nuclei of the facial nerve of both sides, while the lower facial muscles receive their innervation only from the nuclei of the same side. This may explain why the lower facial muscles of one side may be paralyzed without any involvement of the upper facial muscles. Pearson believes that there is still much to be learned about the anatomy and physiology of the components of the seventh nerve.

ADDISON, Philadelphia.

ON THE SIGNIFICANCE OF FISSURATION OF THE ISOCORTEX. P. J. HARMAN, J. Comp. Neurol. **87**:161 (Oct.) 1947.

Harman has brought together measurements, made previously by himself and others, on the dimensions of the cerebral cortex in five mammalian forms—galago (a lemuroid), cat, mangabey (a monkey), chimpanzee (an ape) and man. These forms represent progressive fissuration of the cerebrum in brains of increasing size. For each of these five forms, data are available for the volume of the entire brain, the volume of the isocortex and the average thickness of the isocortex. By dividing the volume of the isocortex by its thickness, a figure is obtained for the area of the isocortex. Harman compares each of the three variables of the isocortex (thickness, surface area and volume) with brain volumes in the form of graphs. These comparisons confirm previous opinions that cortical thickness increases but little in the phylogenetic scale and that fissuration is associated with a great increase in surface area. The new point demonstrated is that the increase in cortical volume is proportionate to the increase in brain volume. This observation is at variance with the usual statement that the cortical folding is due to the proportionately greater increase in the amount of cortex as compared with the increase of the whole brain. The six-layered cortex increases phylogenetically by the addition of new cells side by side with the previous ones, and very little in thickness.

ADDISON, Philadelphia.

SPECIFIC DEVELOPMENTAL INHIBITIONS PRODUCED IN AMPHIBIAN EMBRYOS BY A NITROGEN MUSTARD COMPOUND. ROY GILLETTE and DIEDRICH BODENSTEIN, J. Exper. Zool. **103**:1 (Oct.) 1946.

Embryos of Triturus torosus (stage 36) were exposed forty-five minutes to a 0.001 per cent solution of a nitrogen mustard compound (methyl-bis-[chloroethyl] amine hydrochloride). This chemical agent affected mitotic processes within proliferating cells without retarding histologic differentiation.

In those regions of the neural tube and eye where histologic differentiation occurs in nonmitotic cells, differentiation proceeded at the same pace as in control embryos. However, in the germinal regions of these organs (ependymal layer of the neural tube and the rim of the iris in the eye) mitosis was inhibited for about ten days, whereas the cells continued to grow. Mitosis, when it finally occurred, resulted in disruption of the cells and the destruction of the germinal regions.

A large number of mitotic cells did not exhibit this characteristic reaction but broke down completely within five days of exposure. Such cells were concluded to be still undergoing the cleavage type of mitosis. The characteristic reaction to exposure of the germinal cells showed that they were already physiologically set aside from the cleavage type of mitotic cell, although at that early stage they could be identified only by position.

Fully developed organs suffered less destruction than those which were in a more primitive state. For example, cranial cartilages and sensory ganglia were little affected, whereas trunk cartilages and sensory ganglia were completely suppressed.

The selective action of the agent on mitosis, but not on differentiation, was demonstrated by the reaction of gut and epidermal cells when these two processes occur in the same cell. Although mitosis was stopped, the cells continued to grow and became abnormally large. However, in these enlarged cells the characteristic histologic differentiation occurred at the same time as in the smaller cells of the unexposed animals.

The nitrogen mustard compound not only revealed centers of proliferation but arrested proliferating organs in various stages of development. Organs of various sizes, depending on their developmental condition at the time of exposure, could thus be produced.

REID, New Brunswick, N. J.

QUANTITATIVE STUDIES ON THE LOCOMOTOR CAPACITY OF LARVAL AMBLYSTOMA (A. JEFFERSONIANUM) LACKING MAUTHNER'S NEURON OR THE EAR. S. R. DETWILER, J. Exper. Zool. **104**:343 (April) 1947.

By the use of a quantitative method, the locomotor capacity of young larvae lacking either one Mauthner neuron or one ear was compared with that of normal controls in similar stages of development. The locomotor tests were made beginning with stage 38 and ending seven days after the feeding stage (feeding began at a period similar to stage 44 of Amblystoma punctatum). At stage 39 the scores (total number of units covered in twenty-five stimulations) rose markedly for all three groups. The larvae lacking an ear made the lowest scores in early stages (38 to 43), but their locomotor capacities rose to equal those of the controls at the termination of the experiment. The larvae lacking the Mauthner neuron showed a steady decline in their motor responses up to two days after the feeding stage, when the scores leveled off.

Histologic examination established the fact that only the Mauthner cell was absent after unilateral excision at stage 23. In larvae with low scores in which Mauthner's cell was not excised, the normal function of the cell may have been disturbed as a result of the operation.

These observations on young larvae support the former conclusions that, while Mauthner's neuron is not indispensable for normal equilibration, it is essential in facilitating the cephalocaudal progressing flexures involved in normal swimming.

REID, New Brunswick, N. J.

THALAMIC DEGENERATION FOLLOWING BILATERAL PREMOTOR FRONTAL LOBE ATROPHY OF THE STRÜMPELL TYPE. R. M. NORMAN, J. Neurol., Neurosurg. & Psychiat. **8**:52 (Jan.-April) 1945.

Norman reports the case of an imbecile epileptic girl who died in her nineteenth year. The brain showed bilaterally symmetric atrophy of the frontal lobes, exclusive of the precentral gyri. The lesions presented a spongelike appearance, consisting of multiple cavities resembling changes usually seen after phlebostasis or phlebothrombosis as a result of birth injury. Detailed studies of the thalamus revealed retrograde degeneration of the entire dorsomedial nuclei and a reduction of neurons in the medial third of the anterior part of the ventrolateral nuclei. It has been stated that in monkeys the anterior part of the ventrolateral nucleus projects mainly on the precentral gyrus. The findings in this case, however, suggest that in the course of evolution the projection field of the anterior ventrolateral nucleus shifts progressively in a frontal direction.

N. MALAMUD, San Francisco.

Physiology and Biochemistry

STUDIES ON CHOLINESTERASE: VI. KINETICS OF THE INHIBITION OF ACETYLCHOLINE ESTERASE. KLAS-BERTIL AUGUSTINSSON and D. NACHMANSOHN, J. Biol. Chem. **179**:543, 1949.

The study of the kinetics of the inhibition of acetylcholine esterase by two types of inhibitors, reversible and irreversible, has been continued. Tetraethylpyrophosphate was found to inactivate the enzyme irreversibly, and at 10 C. almost immediately, in contrast to diisopropyl fluorophosphate, with which, at this temperature, the irreversible reaction is a relatively slow process. The study of the action of this inhibitor as a function of enzyme concentration has revealed that a considerable excess of inhibitor is necessary, the need increasing with increasing dilution. The enzymatic hydrolysis of acetylcholine in the presence of neostigmine and physostigmine attains an equilibrium which is the same whether or not the enzyme has been incubated with the inhibitor prior to the addition of acetylcholine. No such equilibrium is attained with the irreversible inhibitors tetraethylpyrophosphate and diisopropyl fluorophosphate. If acetylcholine is added to the enzyme simultaneously with the inhibitor, a protective action is observed, suggesting that all four inhibitors act on the same active center of the enzyme. Tetraethylpyrophosphate is by far the strongest of all four inhibitors tested. When the inhibitor effects are studied at various substrate concentrations, neostigmine and, to a lesser degree, physostigmine produce a shift of the optimum substrate concentration. No such shift is observed in the case of the two irreversible inhibitors.

PAGE, Cleveland.

PROTECTION OF GLYCOLYSIS IN MOUSE BRAIN HOMOGENATES BY AMIDES AND ESTERS OF AMINO ACIDS. I. KRIMSKY and E. RACKER, J. Biol. Chem. **179**:903, 1949.

The glycolytic activity of mouse brain homogenates is inhibited by an inactivating factor present in normal brain. This factor requires Fe^{++} and either cysteine or ascorbic acid as activators. A similar inhibition of glycolysis is produced by cathepsin III purified from beef spleen. The inhibition of glycolysis produced by either a cathepsin III preparation or the inactivating factor of brain is prevented by the addition of certain amides and esters of amino acids. Cathepsin III preparations, as well as homogenates of mouse brain, hydrolyze the ethyl esters of *l*-leucine and *l*-cysteine.

PAGE, Cleveland.

A Study of Post-Ischaemic Paraesthesiae. W. R. Merrington and P. W. Nathan, J. Neurol., Neurosurg. & Psychiat. **12**:1 (Feb.) 1949.

Merrington and Nathan investigated the paresthesias which follow a period of circulatory arrest in a limb. They differentiate ischemic paresthesias or those felt during arrest of circulation from postischemic paresthesias or those felt after release of the circulation. Four components of the latter are described: (1) thermal, (2) tingling, (3) pseudocramp and (4) pricking sensations, the paresthesias usually appearing in that order when circulation is released to an ischemic limb. The method used was occlusion of the circulation with a blood pressure cuff. The duration for which the limb was rendered ischemic was the most important factor in determining the character, duration and distribution of the paresthesias. The position of the cuff on the limb, which determined the amount of the limb made ischemic, was also important in that the more proximal the cuff, the more readily were the paresthesias produced. Reduction in temperature prior to application of the cuff produced diminution in tingling and accentuation of pricking. In an attempt to locate the site of origin of the postischemic paresthesias it was shown that neither the sensory end organs nor the nerves distal to the segment compressed by the cuff are essential for production of the sensations, but that they arise in the larger nerves directly beneath the clamp when the circulation is restored to them. Nevertheless, recovery from ischemia in all parts of a nerve contributes to the sensations. The nerve fibers conducting these sensations are those for touch (tingling), firm pressure (pricking) and position and movement (pseudocramp) sensibility. Fibers conducting pain and temperature sensation and sympathetic fibers play no part. Within the central nervous system, paresthesias are conducted in the posterior columns of the cord.

N. Malamud, San Francisco.

The Effect of Diisopropyl Fluorophosphonate of Neuromuscular Transmission in Cats. G. L. Brown, B. Delisle Burns and W. Feldberg, J. Physiol. **107**:346, 1948.

In decerebrate cats (2 to 3 Kg.) the arterial injection of 100 to 200 micrograms of diisopropyl fluorophosphate (D F P) causes an increase in tension response of the musculus tibialis anterior to single maximal motor nerve volleys. This potentiation is due to repetitive contraction of the muscle fibers and is followed by a period of depressed response, during which the contraction is still repetitive. By intravenous injection, diisopropyl fluorophosphate is effective only in very large doses (10 mg. per kilogram).

During and after the potentiation with diisopropyl fluorophosphate, stimulation of the nerve at 50 to 200 cycles per second for five to ten seconds produces a poorly sustained contraction, which is followed by a transient depression of the response to single nerve volleys; a similar, but more permanent, depression of the response to single nerve volleys is produced by an arterial injection of acetylcholine.

The depressant effects observed after injection of diisopropyl fluorophosphate results from an action of acetylcholine which produces neuromuscular block and a condition of inexcitability of the muscle fiber, both when the acetylcholine is injected or when it is released at the nerve endings.

On the denervated muscle an arterial injection of even 2 mg. of diisopropyl fluorophosphate has no effect. A subsequent injection of acetylcholine produces a contraction which is greater and more prolonged than that which occurs in the untreated muscle; it is followed by a profound depression of the response of the muscle to direct electrical excitation.

The fact that diisopropyl fluorophosphate has a greater affinity for pseudocholinesterase than for true cholinesterase must be taken into account when the effect of arterial and intravenous injections of diisopropyl fluorophosphate on neuromuscular transmission are compared with those of physostigmine.

THOMAS, Philadelphia.

BRADYCARDIA OF CENTRAL ORIGIN PRODUCED BY INJECTIONS OF TETANUS TOXIN INTO THE VAGUS NERVE. N. AMBACHE and O. C. J. LIPPOLD, J. Physiol. **108**:186, 1949.

The injection of tetanus toxin into the central end of one vagus nerve produces in rabbits cardiac slowing and arrhythmia. This localized symptom appears after a latent period of twenty-two to forty-three hours and terminates in death from heart failure within a few hours, unless the remaining intact vagus nerve is cut. The same effect could be produced by injecting the toxin (*a*) into an uncut vagus nerve, or (*b*) subperitoneally in the vicinity of the vagus, either in its esophageal portion or on the anterior wall of the stomach. The action is specific and could, in all three types of injection, be prevented by tetanus antitoxin.

The cardiac slowing is due to an overactivity of the vagus nerve. It is removed by vagotomy or by local anesthesia of the vagus nerves in the neck. It can also be abolished for a time (*a*) by a peripheral block of the vagus nerves with atropine, and (*b*) by depression of the vagus center with pentobarbital sodium in anesthetic doses. The analysis of this effect shows that the bradycardia is probably due to a central action of tetanus toxin on the cardioinhibitory center.

THOMAS, Philadelphia.

PRESSOR RESPONSES TO ELECTRICAL STIMULATION OF THE CAROTID SINUS NERVE IN CATS. E. NEIL, C. R. M. REDWOOD and A. SCHWEITZER, J. Physiol. **109**:259, 1949.

BLOOD-PRESSURE RESPONSES TO ELECTRICAL STIMULATION OF THE CAROTID SINUS NERVE IN DOGS AND RABBITS. E. NEIL, C. R. M. REDWOOD and A. SCHWEITZER, J. Physiol. **109**:281, 1949.

The authors studied the effects on blood pressure of stimulating the carotid sinus nerve. Results in cats are reported in the first communication (page 259) and those in dogs and rabbits in the second (page 281). They used various anesthetics and stimulating currents of different strengths, durations and frequencies. It will be recalled that the carotid sinus nerve contains pressor fibers from the chemoreceptors of the carotid body and depressor fibers from the pressure receptors (baroceptors) of the carotid sinus. The study was, in essence, an investigation of the differential excitability of the pressor and depressor fibers and of the effects of anesthetics on the responsiveness of the vasomotor center in the several species studied.

Stimulation of the carotid sinus nerve trunk in cats under anesthesia produced with chloral hydrate and dextrose (chloralose) by means of an induction coil or a rectangular wave electronic stimulator with pulses of short duration (0.05 to 0.1 millisecond) caused decided rises in arterial blood pressure and hypernea, but only insignificant changes in heart rate. Pulses of longer duration (0.5 to 1.0 millisecond) occasionally caused a fall in blood pressure. These effects involved the activity of the vasomotor center. Stimulation of the carotid sinus nerve in unanesthetized decerebrate cats, in cats under phenobarbital anesthesia or in cats under chloral hydrate anesthesia invariably lowered the blood pressure, irrespective of the duration of the stimulus used. Subsequent intravenous injection of chloralose

in such animals converted the previous depressor response to stimulation into a pressor response. Responses to rises of intrasinusal pressure in cats under phenobarbital anesthesia were diminished by intravenous injection of chloralose. In addition, perfusion of the isolated carotid sinus with Ringer-Locke solution containing chloralose diminished the response to increase in hydrostatic pressure. Chloralose diminishes in cats the sensitivity of the vasomotor center and of the baroceptors of the carotid sinus to changes in intrasinusal pressure.

Electrical stimulation of the carotid sinus nerve trunk in rabbits and dogs under chloralose and phenobarbital anesthesia, using a rectangular wave electronic stimulator or an induction coil, produced marked depression of the arterial blood pressure. Variations in frequency and in the pulse duration of the stimuli did not alter the direction of the blood pressure response. Injection of chloralose into rabbits and dogs under phenobarbital anesthesia did not modify the nature of the blood pressure response to electrical stimulation of the sinus nerve. THOMAS, Philadelphia.

ACTION OF D-TUBOCURARINE CHLORIDE ON FOETAL NEUROMUSCULAR TRANSMISSION AND THE PLACENTAL TRANSFER OF THIS DRUG IN THE RABBIT. A. J. BULLER and I. MAUREEN YOUNG, J. Physiol. **109**:412, 1949.

The use of curare in operations on pregnant women, particularly cesarean section, raises the question of possible depression of neuromuscular excitability in the fetus. To assess this danger, the authors studied the susceptibility of fetal tissues to the action of curare and the placental transmission of curare from mother to fetus. Rabbit, guinea pig, rat and human fetuses were studied. Neuromuscular transmission is blocked in the fetus by curare, as in the adult. This effect is reversed by neostigmine and potassium salts, as in the adult. However, the placenta provides an effective barrier to the transfer of curare from mother to fetus, at least in therapeutic doses. A concentration of 140 micrograms per milliliter was required to cross this barrier. Therapeutic doses produce concentrations of the order of 3 micrograms per milliliter.

THOMAS, Philadelphia.

ORIGIN OF THE ACETYLCHOLINE ESTERASE IN THE PATHOLOGIC SPINAL FLUID. M. WOLLEMAN and I. HUSZAK, Wien. klin. Wchnschr. **61**:90 (Feb. 11) 1949.

Wolleman and Huszak show that there is an increase of specific caffeine-inhibited acetylcholine esterase in a pathologic spinal fluid with high albumin content only when destruction of nerve tissue is taking place. A study of 50 abnormal spinal fluids shows the absence of the caffeine-inhibiting phenomenon in cases of meningitis, polyneuritis, polyradiculoneuritis, cerebrospinal syphilis, meningoencephalitis and multiple sclerosis. Inconsistent results were obtained in cases of polyomyelitis, in which only after seven or eight days was specific caffeine-inhibited acetylcholine esterase found. Definite caffeine inhibition was found in cases of dementia paralytica before malarial therapy, of encephalomalacia and of malignant brain tumors. In cases of dementia paralytica a certain relation between the caffeine inhibition and the clinical picture was present; in a case in which the highest inhibition values were found, the patient died within a few days.

MASON, New York.

THE BLOOD SUGAR LEVEL IN THE DIAGNOSIS AND PROGNOSIS OF CEREBRAL CONCUSSION. JOHANNES EBERLE, Wien. klin. Wchnschr. **61**:120 (Feb. 25) 1949.

In over 300 cases of cerebral concussion systematic blood sugar determinations were made. Fasting samples were examined daily after hospitalization and then twice weekly. The results were then plotted to form a curve.

One group of patients showed a "lytic" blood sugar curve. After a rapid increase, the values returned to normal "by lysis" within a few weeks, and so did the signs and symptoms of concussion. A follow-up of these patients showed that 44 per cent of them were symptom free, 43 per cent had mild complaints which did not interfere with their ability to work and 13 per cent were limited in their work because of symptoms. The last group comprised patients who, owing either to lack of insight into their condition, or to environmental stresses, had to resume work immediately after discharge from the hospital. In a general way, children did not show changes in the blood sugar level, or they appeared to fall into this "lytic" group.

A second group of patients showed an "undulant" curve. There was little change in the blood sugar up to the fifth, and sometimes to the eighth, day. From then on the blood sugar level fluctuated, usually above the norm, only rarely showing hypoglycemia. These patients complained for a long time of headaches, dizziness, insomnia, and the like. The follow-up of this group showed that 12 per cent of the patients were symptom free, 38 per cent were fully employed, although having complaints, 42 per cent were limited in their work by their complaints and 8 per cent were totally disabled.

After the patient sat up or got out of bed, the blood sugar value for the "lytic" group rose suddenly but returned quickly to normal value. The "undulant" group showed a slight increase, which, however, persisted for a long time.

MASON, New York.

VARIATIONS IN BROMINE CONTENT OF THE BLOOD AFTER ELECTRIC SHOCK. C. I. URECHIA, I. COSMULESCU and D. MICOU, Confinia neurol. **9**:392, 1949.

Urechia, Cosmulescu and Micou analyzed the alterations in the bromine level of the blood before and after electric shock therapy, using Walter's method. Seven patients with manic-depressive psychosis and 8 with dementia precox were the subjects of the study. The bromine levels were determined immediately before, immediately after and one-half hour and one hour after the induced shock. Sleep after the shock was always associated with a rise in the bromine level. In all cases there was either a rise or a fall.

FOLEY, Boston.

Neuropathology

THE MOTOR CORTEX IN AMYOTONIA CONGENITA. WALTER FREEMAN, J. Neuropath. & Exper. Neurol. **5**:207 (July) 1946.

Freeman reports the case of a girl aged about 4 months who from the time of birth had never moved her legs and who showed only slight movements of the arms. The cry was weak and husky. Nursing was difficult, and the child had to be stimulated constantly to suck; exhaustion developed quickly on effort. The child remained in the hospital for about three months and made little or no progress. At home, a good state of nutrition could not be maintained, and she was hospitalized because of increased temperature, dyspnea and cyanosis. Examination showed a deep funnel deformity of the chest with retraction of the intercostal spaces at each inspiration, the respiration being purely diaphragmatic. The lower limbs were flaccid, and the upper ones, almost so, although there was a little tone in the biceps and the fingers were contracted in flexion. No tendon reflexes were obtained. The corners of the mouth were turned downward; they showed moderate retraction during crying, which was almost soundless. Sucking was weak and

soon exhausted. Mucus had to be aspirated from the pharynx and larynx, since the child could apparently neither swallow nor cough it up. Even in a respirator with oxygen the child grew weaker and died within twenty-four hours.

Necropsy was performed, and Freeman observed that the pathologic alterations in the central convolutions in 3 other cases, in which there was complete necropsy, were identical with those in the present case. In 2 other cases which he had studied the material available to him was insufficient. Freeman's studies indicate that the cortical changes in amyotonia congenita are definite, but they have attracted little notice heretofore. He states, "While the deficiency of ganglion cells was spectactular only in respect to the giant multipolar cells of Betz, it was still fairly obvious in layer III and even in layer I. The cortex was also immature in the arrangement of cells, a tendency to columnar orientation being observed. In the matter of individual configuration, the "Betz" cells in amyotonia were relatively undeveloped. They showed a pyramidal rather than polygonal shape, with prominent vesicular nuclei but little chromatin material, few processes and no definite neurofibrils. No degenerated cells were seen; they were rather of the immature type. The feltwork of processes in the vicinity of these cells was more delicate than that seen in the control case.

"Comparison of the postcentral convolutions of the amyotonia case with the normal also showed pronounced immaturity, the cells being fewer in number, especially in layers III, IV and VI, and tending to be arranged in columns. Layers I, II and V were less strikingly altered. No other deficiencies were noted in the central nervous system and there was no deposit of fat to suggest parenchymatous breakdown. . . .

"This may prove to be an important point in differentiating this disease pathologically from infantile spinal muscular atrophy."

GUTTMAN, Wilkes-Barre, Pa.

SUBARACHNOID AND VENTRICULAR IMPLANTS IN EPENDYMAL AND OTHER GLIOMAS. I. M. TARLOV and L. M. DAVIDOFF, J. Neuropath. & Exper. Neurol. **5**:213 (July) 1946.

The spread of malignant gliomas, particularly medulloblastomas, in the subarachnoid space is well known, but the occurrence of subarachnoid implants of ependymal tumors has been infrequently reported. Tarlov and Davidoff present reports on 3 patients with spinal subarachnoid implants in association with intracranial tumors of ependymal origin.

One patient was a woman aged 39 who had an ependymoma of the posterior fossa removed at operation. About a year later a spinal implant was verified by operation. Roentgen radiation to the brain and spinal cord was administered. The patient died as a result of vesical and renal infection secondary to transverse compression of the spinal cord four years after the first operation.

This case illustrates the two ways in which gliomas may spread. The extension of tumor from the vermis along the subarachnoid space for an unknown distance down the spinal canal is by continuity. The presence of discrete nodules of tumor tissue within the spinal arachnoid space, as disclosed at the time of laminectomy, indicates spread of the tumor by implantation along the subarachnoid space, the tumor cells having been conveyed by the cerebrospinal fluid. The proximity of the primary tumor to the subarachnoid spaces would appear to be almost as important a factor in the "seeding" of the tumor within the cerebrospinal fluid pathways as the malignancy of the tumor itself, particularly in view of the occurrence of spinal implants in gliomas composed of differentiated, as well as of

embryonic, cell types. However, implantations are more frequent in the more undifferentiated gliomas.

The second patient was a girl aged 11 years who had an ependymoblastoma of the cerebellum with diffuse cerebral and spinal subarachnoid implantation. The first symptoms appeared one month prior to her admission to the hospital, and there were neurologic signs of involvement of the cerebellum and brain stem. Suboccipital exploration was performed, and a biopsy of the tumor was performed. The patient died on the fifth postoperative day. In this case the subarachnoid implants of the tumor were identical with the primary cerebellar tumor. The implants had grown through the pia and invaded the parenchyma of the cerebrum, pons and spinal cord. The tumor was rather undifferentiated. The presence of many areas in which there was a striking perivascular pattern and in which the cells proved to be ependymal spongioblasts would seem to warrant designation of the tumor as an ependymoblastoma. The fact that the patient died five days after this neurosurgical procedure excludes the possibility of seeding of gliomas after operation.

The third patient was a girl aged 10 years in whom an ependymal tumor of the right parieto-occipital region was removed at operation. A recurrent neoplasm was removed two years later, and five months after this evidence of involvement of the spinal cord appeared. A spinal subarachnoid tumor was verified at operation. The patient died three years after the first operative procedure.

Tarlov and Davidoff, in the series of cases reported in this study, encountered 8 cases in which tumors of ependymal origin occurred. Subarachnoid spinal implants were encountered in 3 of them; in 2 cases symptoms referable to the implant appeared, and temporary clinical improvement followed its removal in 1 case. However, anterolateral chordotomy had to be done in order to afford relief from pain, which was the result of extensive seeding of the tumor in the spinal subarachnoid space.

Ventricular or subarachnoid implants may occur in association with practically all types of gliomas, benign as well as malignant, although much more commonly with the latter. The authors stress the fact that when distant cerebral or spinal symptoms or signs occur in association with gliomas of ependymal or other origin, benign as well as malignant, the possibility of subarachnoid implants from the original tumor must not be overlooked.

Discrete subcutaneous nodules of glioma tissue were encountered at necropsy in the scalp flap of a patient from whom a glioblastoma multiforme was removed eight months before death. Cerebral tumor implants were present in this patient also.

GUTTMAN, Wilkes-Barre, Pa.

RAPID PRODUCTION OF ACUTE DISSEMINATED ENCEPHALOMYELITIS IN RHESUS MONKEYS BY INJECTION OF BRAIN TISSUE WITH ADJUVANTS. ELVIN A. KABAT, ABNER WOLF and ADA E. BEZER, Science **104**:362 (Oct. 18) 1946.

Rapid production of acute disseminated encephalomyelitis was achieved in 4 rhesus monkeys. The animals received an emulsion of 18 Gm. of rabbit brain in 20 cc. of saline solution, 20 cc. of "aquaphor" (an oxycholesterol-petrolatum ointment base) and 40 cc. of liquid petrolatum U. S. P. containing 95 mg. of dried, heat-killed tubercle bacilli. A second group of 4 monkeys received an emulsion of 27 Gm. of rabbit lung prepared in a similar manner. Both brain and lung materials contained phenol in a final concentration of 0.25 per cent and were heated to 60 C. for forty-five minutes to destroy autolytic enzymes. Each monkey received three intramuscular injections of 1 cc. of material into the arm or leg at weekly intervals.

Three of the 4 monkeys receiving inoculations of brain tissue became ill from twenty-five to thirty-three days after the first inoculation, or nine to nineteen days after the last injection. At first the animals were less responsive than usual, and soon thereafter focal signs of damage to the central nervous system appeared and progressed. The localization, sequence of appearance and speed of development of the signs varied in the 3 animals. The 3 affected monkeys were killed by exsanguination on the day of the appearance of symptoms and two to eight days thereafter, respectively. Blood cultures proved sterile. Culture of cerebral tissue from 1 of the monkeys and intracerebral and intraperitoneal inoculation of a brain suspension into 3 mice and a rabbit did not produce the disease.

Postmortem studies revealed lesions limited almost exclusively to the central nervous system. The lesions were focal, vascular and perivascular and were most marked in the brain stem, particularly in the pons and the cerebellum. There was a decided predilection for the white matter, with a tendency to periventricular clustering.

A survey of the cytopathologic changes makes it clear that in the 3 monkeys there was rapidly produced a condition resembling acute disseminated encephalomyelitis, marked by demyelination. This was achieved by the use of adjuvants added to rabbit brain emulsions.

No symptoms were observed in the fourth monkey given injections of brain material, nor were abnormal signs noted in any of the animals which had received the emulsion of lung tissue.

The fact that adjuvants enhance the effect of brain tissue in producing this pathologic process supports the hypothesis that an antigen-antibody reaction is involved in the formation of the lesions. This is also indicated on histologic grounds by the abundant histiocytic response and is indirectly corroborated by the absence of lesions in other organs; its specificity for brain is evidenced by the failure to produce the same results with lung tissue.

GUTTMAN, Wilkes-Barre, Pa.

THE CENTRUM MEDIANUM THALAMI IN SENESCENCE AND IN SENILE DEMENTIA. K. SIMMA, Monatsschr. f. Psychiat. u. Neurol. **118**:44 (July) 1949.

This report represents an attempt by the author to investigate the allegations made by C. and O. Vogt that a uniform primary degeneration of the centrum medianum takes place in nondemented aged persons. The Vogts studied 4 brains of senescent nondemented persons and 5 brains of persons with senile dementia and noted blanching of the nerve cells and increase in the glia cells which they attributed to a "topistic" degeneration of the centrum medianum.

Simma studied the brains of 2 nondemented aged persons and of 7 patients with senile dementia; of these, 3 were over 85 and 4 over 90 years of age. In addition, the brains of 3 patients with Pick's or Alzheimer's disease were examined histologically. The findings were not specific. There was considerable variation in the size and coloration of the ganglion cells, changes which might be related to nutritional deficiency, as well as to the time elapsing between death and fixation of the tissues. Many of the cells were pale and not too sharply outlined, although they presented no pathologic cellular alterations. In no case was there evidence of a considerable loss of ganglion cells, and no increase in the glia fibers was discernible with the Holzer method. Comparison of this material with sections of the brains of younger subjects disclosed no differences. The centrum medianum in cases both of Pick's and of Alzheimer's disease were better stained than that in cases of senile dementia, but no pathologic changes were noted.

PISETSKY, New York.

Psychiatry and Psychopathology

PERSONALITY CHANGE AFTER PREFRONTAL LEUCOTOMY. L. FRANKL and W. MAYER-GROSS, Lancet **2**:820 (Dec. 6) 1947.

Frankl and Mayer-Gross report on a follow-up questionnaire on 68 patients who had had prefrontal leukotomy and had been home for at least six months. Fifty-one patients had had long-standing schizophrenia, of the catatonic or paranoid type; 9, obsessional neurosis; 7, melancholia, and 1, recurrent manic attacks. Letters were sent both to the patients and to their relatives. More than half the patients could earn their living, and more than three fourths were usefully employed. More than one half had the same occupation as before; the others had gone down in the occupational scale.

From the replies, the authors sketched a composite character of a patient after leukotomy:

"The patient is physically healthy, a good eater and sleeper, with considerable euphoria. His prevailing mood is cheerfulness; he does not worry, is happy and contented, and shows it. He has a high opinion of himself and his abilities. He may take his responsibilities too easily or may shirk them altogether. He leads an active life, is restless, and likes movement and change. His interests and hobbies are varied and variable, with a preference for light entertainment and superficial pastimes. He is easy-going, a good mixer and fond of social life and of being on good terms with everybody.

"On the other hand, his relations with the people round him are often without depth of feeling. He shows little sympathy or consideration for his next of kin or anybody else. He neither regrets nor repents whatever he may have done or said. He may be self-willed, headstrong, and unable to see the other person's point of view. He tends to quickly passing outbursts of temper. He may attend to his work as before or may do less well, but he invariably thinks he does well; he is not a perfectionist."

In clinical terms, the main features of this composite picture are symptoms of damage to the frontal lobe after head injury or lobectomy for tumor.

As for the selection of patients for leukotomy, the condition of hebephrenic patients showing only lack of initiative, affective blunting and facetiousness is too much akin to the frontal syndrome to permit any improvement. The operation is very helpful in cases of severe obsessional illness. In a small number of patients with chronic affective psychoses, periodicity has been abolished and more than three fourths of them have recovered. Of the schizophrenic patients, excluding the hebephrenic type, 30 to 40 per cent were restored to a useful life and 20 to 30 per cent had definite improvement in their most distressing symptoms.

With the exception of quickly deteriorating patients with "nuclear" schizophrenia, the authors state that all patients should have the usual less drastic therapies and that, if this fails, the psychosis should be left to run its course as long as a spontaneous remission can reasonably be expected.

In postoperative care, the authors believe that this follow-up has strengthened the case for a prolonged convalescence in hospital before discharge, a minimum of three months. "There is no doubt that these patients who have been patiently and tactfully supervised at home have adapted best; on the other hand, most of the readmissions were due to lack of understanding and guidance in the home and to other adverse environmental factors."

There were no reports of any serious conflict with law and order, and restraint in sexual matters was the rule; for 1 man only was excessive sexual indulgence reported. Almost half the patients were still improving, some of them two years after the operation.

MADOW, Philadelphia.

SIGNIFICANCE OF HORMONAL DISTURBANCES FOR DEVELOPMENT OF MENTAL DISEASES: A REVIEW. A. LETH PEDERSEN, Acta endocrinol. **1**:230, 1948.

Leth Pedersen discusses mental symptoms in association with endocrine lesions. He suggests that certain mental disorders may have an endocrine basis. He is concerned particularly with women, giving an account of studies concerning patients with lesions in or about the hypothalamus and women castrated by operation. Both groups of patients show symptoms of emotional instability and increased irritability, but these are not identical in the two groups. The patients with hypothalamic lesions show, in addition to emotional instability, decided egocentricity, with a tendency to be hard to please, inert and despairing, whereas women who have undergone castration do not show these tendencies but are restless and inclined to minimize their symptoms.

J. A. M. A.

Diseases of the Brain

SIGNIFICANCE OF THE WIDENED SEPTUM PELLUCIDUM. R. M. LOWMAN, R. SHAPIRO and L. C. COLLINS, Am. J. Roentgenol. **59**:177 (Feb.) 1948.

Widening of the septum pellucidum is an important abnormal finding, which demands investigation. Significant widening of the septum may be produced by the following conditions: (1) cysts of the cavum septi pellucidi, (2) tumors of the septum pellucidum, (3) agenesis of the corpus callosum and (4) tumors of the corpus callosum. Other lesions which may arise in the differential diagnosis are tumors of the third ventricle, pinealomas, tumors of the lateral ventricle, midline tumors of the frontal lobe, olfactory groove meningiomas, parasagittal tumors and thalamic tumors. The thalamic group, however, can usually be distinguished and differentiated from the lesions of the third ventricle.

The cysts of the septum pellucidum and the cavum vergae are communicating or noncommunicating. The former are well filled with air during the contrast studies and offer no great problem in diagnosis. Roentgenologically, the noncommunicating cysts cannot be distinguished from a solid tumor of the septum pellucidum. Tumors of the septum pellucidum are rare and are usually gliomas, most commonly astrocytomas. There are no characteristic or neurologic findings. The roentgenologic picture, however, is fairly characteristic. There is widening of the septum pellucidum and separation of the lateral ventricles, together with pressure defects on the medial walls of the ventricles. Since primary tumors of the septum and noncommunicating cysts may produce a similar roentgenologic appearance, the authors suggest a trocar puncture of any mass lesion in the septum pellucidum, thus allowing air to enter the lesion if it is a noncommunicating cyst. In this way, it becomes a communicating cyst and can readily be distinguished from a tumor roentgenologically.

The authors report 3 cases of tumor of the septum pellucidum, 2 of which were of astrocytomas; both the patients died. In the third case, though biopsy was performed, the tumor was inoperable, and the patient was given a course of roentgen therapy. The patient was still alive and fairly well six years after operation. The diagnosis in this case was oliogodendroglioma. In this case the tumor not only separated the ventricles but produced pressure on the foramen of Monro, giving rise to dilatation of the lateral ventricles. In all these cases it was practically impossible to distinguish roentgenologically between a tumor and a noncommunicating cyst.

The neurologic complaint and findings were not characteristic of any particular localization. In 1 case the symptoms consisted of headaches, projectile vomiting,

episodes of unconsciousness and impairment of memory with some personality changes. In another case the symptoms were intermittent headaches for nine years, a generalized epileptic seizure, impaired hearing in the right ear and symptoms of increased cranial pressure, the last appearing about three weeks before the patient's admission. In the third case there were headaches for six months, a painful sensation over the eyes, weakness with difficulty in walking and ringing of the ears.

In agenesis of the corpus callosum, characteristic pneumographic changes were described by Davidoff and Dyke. Occasionally agenesis of the corpus callosum may be associated with midline intracranial lipoma. However, agenesis has been misinterpreted as a cyst of the septum pellucidum in a number of cases.

Tumors of the corpus callosum are rare. Dyke and Davidoff enumerated the characteristic pneumoencephalographic findings as follows: "(1) separation and asymmetrical distortion of the lateral ventricles without displacement of the ventricular system as a whole to either side; (2) a sharply circumscribed defect in the dorsal margin of one or both lateral ventricles; (3) occasional failure of one lateral ventricle to fill with gas; (4) distortion of the sulci and convolutions on the medial aspect of the brain; (5) deformity or obliteration of the dorsal and rostral portions of the third ventricle." The asymmetric, irregular separation of the lateral ventricles produced by callosal tumors is of the greatest aid in distinguishing these lesions from lesions of the septum pellucidum. Also, the deformity of the dorsal aspect of the lateral ventricles and the changes in the callosal and cingulate sulci seen with callosal tumors in the lateral view are not found in cases of cysts of the septum pellucidum.

Tumors of the third ventricle, pinealomas, tumors of the lateral ventricle, midline tumors of the frontal lobe, olfactory groove meningiomas, parasagittal tumors and tumors of the thalamus, while they may all produce changes in the lateral ventricles and may also lead to separation of the two ventricles, practically never separate the lateral ventricles symmetrically and for the entire depth of the septum pellucidum. Usually it is not difficult to distinguish these lesions from a primary lesion of the septum pellucidum.

J. G. TEPLICK, Philadelphia.

NEUROLOGICAL SYNDROMES IN TYPHUS. E. HALPERN, J. Nerv. & Ment. Dis. **1**:25 (Jan.) 1949.

Halpern reports various neurologic syndromes from several thousand cases of typhus. There were few gangrenous complications and many cases of encephalitis. He stresses the fact that the inflammatory process involves the entire central nervous system, the meninges and often the peripheral nervous system. He describes twenty-two heterogenous syndromes, including meningoencephalitis, bulbar involvement, encephalitis extrapyramidalis, cranial neuritis, peripheral neuritis and involvement of the vegetative and endocrine systems. The spinal fluid protein is increased; the globulin content is normal or slightly increased; pleocytosis is insignificant, and the Weil-Felix reaction is frequently positive. Usually the neurologic and mental manifestations occur when the exanthem appears. The prognosis is graver when these manifestations appear after defervescence.

FARMER, Philadelphia.

EXTRADURAL HEMORRHAGE AS A CAUSE OF CORTICAL BLINDNESS. A. N. GUTHKELCH, J. Neurosurg. **2**:180 (March) 1949.

Guthkelch reports a case of cortical blindness due to bilateral extradural hematoma. A woman, aged 67, fell and struck the occipital part of her skull. She was admitted to the hospital on the following day because of drowsiness and irritability.

Roentgenograms showed a fissured fracture extending from the foramen magnum to the lambda and crossing the left lateral sinus. In four days her state of consciousness had improved to the point of her complaining of blindness. Two weeks later she was garrulous and euphoric. She could dimly perceive hand movements but could not count fingers. Both optic disks showed acute edema and hemorrhages. She was incontinent. Seventeen days after the fall trephine holes were made bilaterally in the occipital region, and 120 cc. of black blood clot was removed from the extradural space of this region bilaterally. The exact site of the bleeding was not found. Two days after operation she was mentally clearer and had become continent, and her vision had improved. Two days after this she was able to read a newspaper. When seen one year later, she was in excellent health, was able to thread a needle and do other fine work, and her optic disks showed no elevation.

TOZER, Philadelphia.

THALLIUM POISONING. J. J. G. PRICK, L. MÜLLER, and W. G. SILLEVIS SMITT, Folia neurol. et neurochir. **2**:95 (April) 1949.

The authors divide thallium poisoning into acute, subacute and chronic types. They emphasize the sudden onset of nausea, vomiting, stomach cramps, diarrhea or constipation and unpleasant gastric sensations. There may be disturbances of the carbohydrate metabolism, as evidenced by albuminuria and glucosuria, and such symptoms as subfebrile temperatures, acute rhinitis, bronchitis, conjunctivitis, insomnia, polyneuritis and emotional instability. The reflex changes were more than could be accounted for by involvement of the peripheral nerves alone. The Babinski reflex was often elicited bilaterally. There were frequent irregularities in respiration and circulation, rapid and irregular pulse and psychic changes, characterized by fright, restlessness or delirium and symptoms resembling the Korsakoff syndrome. The most typical finding was the loss of hair over the entire body on the fourteenth to the eighteenth day.

Histologic examination revealed serious changes in the axis-cylinders of the peripheral nerves, accompanied with degenerative alterations in the medullary sheaths. There were swelling and frequent fragmentation of the axis-cylinders. The brains were edematous and showed scattered punctate hemorrhages. There were changes in the cells of the olivary nucleus and chromatolysis in the substantia nigra and the globus pallidus. In cases of serious poisoning the number of ganglion cells in the spinal cord and in the nuclei of the cranial nerves was decreased.

SJAARDEMA, Los Angeles.

DIFFERENTIAL DIAGNOSIS OF VIRUS INFECTION AND INTRACRANIAL TUMORS: CASE OF A TUMOR OF GARCIN. R. ALBERCA LORENTE and J. MORENO GARCIA, Arch. de histol. nor. y pat. **3**:345 (Nov.) 1946.

A white man aged 46 had noted a mass in the left side of the neck a year before he was first examined. The tumor was removed but was not studied histologically. At the time of the operation drooping of the left upper lid was noted. Four months after the operation another mass was noted in the left preauricular region; this was associated with difficulty in hearing. A month before the patient was first seen, difficulty in swallowing appeared and another mass was discovered in the left side of the neck. At no time was there diplopia, headache or vomiting. The first examination revealed almost total internal and external ophthalmoplegia on the left side except for slight movement of the left superior oblique muscle; absence of

the left corneal reflex; motor and sensory impairment of the left trigeminal nerve and impaired taste on the left, but no papilledema or involvement of the long tracts. There was gradual progression to the time of death. A short time before death all the cranial nerves below, and including, the third were involved on the left side. There was definite atrophy of the trapezius muscle and the tongue, but no papilledema was noted at any time. Ventriculographic examination shortly before death showed obliteration of the left lateral ventricle. A roentgenogram of the skull showed enlarged and blurred margins of the sella turcica. Examination of the spinal fluid shortly before death revealed increased protein and only 2 cells per cubic millimeter. Autopsy showed an epithelial tumor at the left side of the base, which compressed the brain but did not invade it. The tumor was considered a malignant neoplasm, probably arising from a branchial cyst. During life a small tumor, probably a melanosarcoma, was seen in the left fundus. Unfortunately, the eye was not examined at autopsy.

The authors emphasize the difficulty of the differential diagnosis of a tumor of this type and virus infections, which occasionally cause polyneuritis of the cranial nerves. In this case the masses in the neck, the strict unilaterality of the syndrome, the absence of remissions and the changes seen in the roentgenograms of the sella and the ventriculogram were all in favor of a syndrome of Garcin due to a tumor at the base of the brain.

N. SAVITSKY, New York.

EXAMINATION OF THE SPINAL FLUID IN ACUTE PSYCHOSES DUE TO AZOTEMIA. J. B. Dos REIS and ORESTES BARINI, Arq. neuro-psiquiat., São Paulo **6**:241 (Sept.) 1948.

The authors report 11 cases of acute psychoses due to azotemia. Five patients died, but permission for autopsy was not obtained. In 6 cases the azotemia was secondary, being due to infection in 4 and to an alcoholic intoxication in 1. Chronic alcoholism was present in 4 of 8 cases in which adequate histories were available. In each case there was an increase in the urea, glucose and chlorides of the spinal fluid, a change considered typical of encephalopathy with azotemia. In 2 cases the spinal fluid showed an abnormal percentage of polymorphonuclear leukocytes, without pleocytosis. In 2 other cases there were increased protein and pleocytosis with complicating septicemia in both cases.

N. SAVITSKY, New York.

Diseases of the Spinal Cord

POLIOMYELITIS LIMITED TO THE MOTOR NUCLEI OF BOTH TRIGEMINAL NERVES. DENIS WILLIAMS, Proc. Roy. Soc. Med. **40**:555 (Aug.) 1947.

After an acute febrile illness eighteen months previously, which was characterized by meningismus and semicoma, and from which he recovered in a few days, a 6½ year old boy was seen with residual inability to chew. There was complete reaction of degeneration in both masseter muscles and no demonstrable contraction of the temporal, masseter or external pterygoid muscles with jaw drop. Power was fairly well preserved in the muscles opening the jaw. No other neurologic signs were obtainable. In the discussion, Douglas McAlpine recalled 4 cases of poliomyelitis with this sequel, in 3 of which other signs of involvement of the brain stem were present initially, and Hollins mentioned a case in which function was recovered.

BERRY, Philadelphia.

Treatment, Neurosurgery

SURGICAL RELIEF OF SPASTICITY IN PARAPLEGIC PATIENTS: II. PERIPHERAL NERVE SECTION, POSTERIOR RHIZOTOMY, AND OTHER PROCEDURES. L. W. FREEMAN and R. F. HEIMBURGER, J. Neurosurgery **5**:556 (Nov.) 1948.

Ambulation is of prime importance in the rehabilitation of paraplegic patients. One of the most frequently encountered difficulties hindering it is the uncontrolled reflex spasms of certain muscle groups in the limbs and abdomen. Freeman and Heimburger report their methods of treating such spasms.

For the relief of adductor spasms of the lower extremities, they use section of the obturator nerve at the obturator canal. For reduction of a contracture deformity in which the achilles tendon had become shortened, section of the sciatic nerve with immediate resuturing gives enough time before reinnervation takes place for correction of the deformity. Section of the nerve was done in the popliteal space. Other peripheral nerves may be sectioned for relief of spasm in the appropriate muscle group. Rhizotomy of the posterior spinal nerve roots has not been satisfactory in the treatment of reflex spasms in paraplegic patients. Injection of 95 per cent alcohol directly into the spinal cord for the relief of massive spasms has been used, especially if decubitus makes anterior rhizotomy impractical. Subarachnoid injection of alcohol is done only as a temporary measure. It has an effect similar to anterior rhizotomy, but of shorter duration. Continuous spinal or caudal anesthesia exerts no permanent effect on spasticity. Sympathectomy has no appreciable effect in lessening the spasticity. Only in cases of gross neglect are destructive orthopedic procedures to the joints justified.

TOZER, Philadelphia.

EFFECT OF STREPTOMYCIN ON COCHLEAR AND VESTIBULAR MECHANISM IN PATIENTS TREATED PRIMARILY FOR RENAL TUBERCULOSIS. H. H. SIROTA and D. H. JONES, Laryngoscope **58**:1287 (Dec.) 1948.

Sirota and Jones present otologic observations on 16 patients who were treated with streptomycin for renal tuberculosis. All were given 1.8 Gm. of streptomycin daily in divided doses of 0.3 Gm. every four hours. Treatment was continued for one hundred and twenty days for all except 3 of the patients, for whom treatment had to be terminated after sixty-six, seventy-six and one hundred and seven days, respectively, because of toxic effects. Symptoms like nausea, tinnitus and dizziness were recorded daily. Audiograms for both bone and air conduction and caloric tests were performed weekly. Follow-up studies were made on some patients up to a year after cessation of treatment. Nausea occurred in 10 of the patients. It varied in severity and did not persist after treatment with streptomycin was stopped. Dizziness or vertigo was the most frequent symptom, occurring in all but 1 patient. It usually commenced about three weeks after the onset of treatment, and it persisted during a follow-up period of six to eleven months in 13 of the patients. There seems to be no correlation between the streptomycin level of the blood and the resultant toxic manifestations; the effect seems to be cumulative. Since it has been realized that the tubercle bacillus becomes resistant to streptomycin after a certain length of time, changes have been made in the dose and in the duration. At the authors' clinic patients are now treated with a daily dose of 1 Gm. for a maximum period of forty-two days. It is hoped that this will reduce the undesirable side effects.

J. A. M. A.

DISCUSSION ON PENICILLIN IN NEUROLOGY. Proc. Roy. Soc. Med. **40**:681 (Oct.) 1947.

Penicillin in Suppurative Conditions of the Brain. SIR HUGH CAIRNS.

Because of the limited ability of penicillin to penetrate any large nonvascular area of infection, special consideration of effective routes of administration must be given to the treatment of cerebral wounds, brain abscess and pyogenic meningitis. In the intrathecal administration of penicillin, an increase in the dose may do harm; it neither increases the persistence of the antibiotic in the spinal fluid nor raises the survival rate for meningitis. Penicillin given subdurally passes rapidly into the blood stream; thus, for purulent pachymeningitis subdural injections must be given every four to six hours. Penicillin given systemically does not pass into the cerebrospinal fluid in adequate amounts, but it has a subsidiary value in the management of most intracranial infections. Six of 11 patients with pachymeningitis were saved. The standard treatment in almost all cases of brain abscess is complete extirpation of the lesion with the aid of penicillin. The author states that penicillin mixed with sulfamethazine (5,000 units per gram) has been insufflated in all clean operative wounds for two years, with a material drop in the incidence of wound infections.

Treatment of Leptomeningitis with Penicillin. DR. HONOR V. SMITH.

Treatment of pneumococcic and other meningitides due to susceptible organisms has consisted in the intrathecal administration of a solution (2,000 units per milliliter) of penicillin, usually by the lumbar route, in doses of 8,000 to 16,000 units once or twice daily for a minimum of five days. Larger doses are no more effectual and may be harmful. In addition, sulfadiazine is given in full doses, and penicillin systemically is used to combat the primary source of infection.

The most frequent complications are spinal block and relapse of the meningitis. In the acute stage of the disease, spinal block occurs presumably from the deposition of fibrinopus or after delayed or inadequate chemotherapy. It has occurred after administration of 50,000 units or more of penicillin by the lumbar route, especially when a concentrated solution is used. Whenever this complication threatens, penicillin is given by cisternal or, preferably, by intraventricular, injection. Relapses are common; they occurred in 16 of the author's 50 cases, and as often as eight times in a single case. Treatment for the relapse is the same as for the original attack, and the prognosis is usually good.

Of 50 cases of pneumococcic meningitis, recovery occurred in 39; in 2 of the fatal cases death was due to other causes, and in 4 others the patients were moribund on admission. Delay in starting treatment was thus the commonest cause of failure in this series.

In the author's limited experience with streptococcic and staphylococcic meningitis the method was the same. In many cases of these infections brain abscess is a complication, in which event the penicillin must be given intraventricularly. Meningococcic infection rarely requires intrathecal injection of penicillin because the sulfonamides give excellent results.

Penicillin in Neurosyphilis. DR. C. WORSTER-DROUGHT.

The therapeutic course established by British and American services in Europe in 1944 of a total of 2,400,000 units is considered inadequate for treatment of neurosyphilis; at least 3,000,000 units for all forms is necessary, and for parenchymatous neurosyphilis the author recommends at least 4,000,000 to 5,000,000 units. Intramuscular injections at three hour intervals is the method of choice. All

patients should receive an initial series of bismuth injections because of the danger of the Herxheimer-Jarisch reaction. Because of the relapses reported in early syphilis, the author uses arsenicals and a bismuth compound conjointly with penicillin: three injections during the week of treatment, followed by twelve injections each of arsenicals and the bismuth preparation at weekly intervals. Penicillin is strikingly effective in treatment of meningovascular syphilis. Dementia paralytica is best treated with penicillin, followed by induction of ten to twelve paroxysms of malaria and, after this, by administration of arsenicals and a bismuth compound until the Wassermann reaction is negative. In tabes no dramatic change follows administration of penicillin, but in some cases lightning pains and gastric crises may be relieved. Primary syphilitic optic atrophy may be arrested in a fair number of cases by malaria, but penicillin alone is not likely to arrest this condition; in combination with malaria and arsenicals it may hasten arrest. It will not be possible to assess fully the final results of penicillin therapy for several years, and amplification of the schemes of treatment may be necessary as further observations are made.

Penicillin and Neurosyphilis. Drs. Nicol and Whelen.

Of a total of 57 patients (42 of whom had dementia paralytica), 14 carefully selected ones were given penicillin alone; 7 received malaria after penicillin; 6 received malaria and penicillin concurrently, and 30 were given penicillin after malaria. The dose was 4,200,000 units of penicillin over a fourteen day period (300,000 units in a single dose per day). Six of the 14 receiving penicillin alone died, 3 of dementia paralytica, 2 of intercurrent disease and 1 of aortic disease. Of the clinical impressions of the results, the most striking was the physical and mental improvement during the actual course of penicillin therapy. No Herxheimer reaction was noted, and no preliminary course of heavy metals or iodine was given.

Berry, Philadelphia.

Encephalography, Ventriculography and Roentgenography

Radiation Necrosis of the Calvarium. John D. Camp and Robert D. Moreton, Radiology **45**:213 (Sept.) 1945.

A review of 2,046 cases of intracranial tumors treated with roentgen radiation, with or without surgical intervention, revealed only 5 instances of radiation necrosis of the calvaria.

Histologically, the lesion is an ischemic, aseptic necrosis of bone, vascular strangulation being due directly to the irradiation. Roentgenographically, the punched-out lesions of aseptic necrosis are not easily distinguished from multiple myeloma and metastatic malignant growths. Differentiation is based on absence of findings in a previous examination of the skull, followed by the appearance of punched-out areas corresponding to the treated regions and absence of other skeletal changes. Biopsy, when possible, is conclusive.

Discovery of the necrosis was made from five to seventeen years after initial roentgen therapy. There were no clinical symptoms referable to the lesion, and the uncovering of the necrosis was incidental to routine follow-up examinations. The non-weight-bearing role of the calvaria may account for the absence of clinical symptoms.

None of the patients received an unusual amount of roentgen radiation. The necrosis is probably commoner than these figures indicate, since many patients

had no prolonged follow-up period, and the lesions of many others may have been classified as metastatic malignant tumors.

The authors emphasize that skull therapy technic should not be modified because of the possibility of postirradiation necrosis, since the latter development produces no clinical symptoms.

TEPLICK, Philadelphia.

EOSINOPHILIC GRANULOMA OF BONE. C. C. DUNDON, H. A. WILLIAMS and T. C. LAIPPLY, Radiology **47**:433 (Nov.) 1946.

The etiologic factor in eosinophilic granuloma of bone is unknown. At present the lesion is considered to be of inflammatory origin, but no causative organism has yet been demonstrated. It occurs more commonly in young men, with the greatest incidence below the age of 20, but it has been reported in persons of all ages. The osseous lesions are usually solitary and involve the skull, pelvis, vertebrae, ribs and long bones. Multiple lesions are not uncommon.

The commonest symptoms are pain, swelling of the soft tissues and tenderness at the site of the lesion. Soft tissue masses may develop over the osseous lesion. Mild systemic manifestations, including fever, anorexia, headache and loss of weight, have been reported. There may be slight leukocytosis and eosinophilia, with an increase in the blood sedimentation rate. The roentgenographic findings are areas of decreased density, usually round, oval or of irregular shape and sharply demarcated from the adjacent normal bones. The lesions may be from 1 to 4 cm. in diameter. There may be sclerosis of the margins of the lesions. A number of the lesions in long bones show periosteal thickening. Swelling of the soft tissue is commonly seen. The disease originates in the medullary portion of the bone.

The microscopic picture varies in different stages. In the early, destructive stage there are foci of necrosis and hemorrhage and a large number of cells, including eosinophilic leukocytes and myelocytes, large mononuclear cells, lymphocytes, plasma cells, neutrophilic leukocytes and multinucleated phagocytic giant cells. Later, the mononuclear cells become vacuolated, and the eosinophils are less prominent or are completely absent. In the final, or late, stage there are proliferation of connective tissue and eventually regeneration of bone. At the stage when the mononuclear histiocyte is prominent there is a great resemblance to Schüller-Christian disease, and it has been suggested that the eosinophilic granuloma is a stage of this disease.

The prognosis of eosinophilic granuloma is usually good, particularly when the lesion is solitary. The treatment reported consists in surgical excision, curettage or irradiation. All three measures have been effective and have hastened the disappearance of the swelling of the soft tissue and the osseous lesion. In irradiation doses of from 400 to 500 or 1,800 r have been used.

TEPLICK, Philadelphia.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Eric Oldberg, M.D., President, in the Chair
Regular Meeting, Jan. 11, 1949

Oligodendroglioma of the Spinal Cord: Report of a Case. Dr. Paul C. Bucy and Dr. John R. Russell.

A. LeC., a white man, had noted scoliosis and fibrillations of the muscles of the back at the age of 17. There then slowly developed clumsiness and weakness of the hands and legs. His symptoms were relieved by a spinal fusion at the age of 25. At the age of 29 he noted loss of sensation in the lower extremities, followed by slowly progressive weakness in the legs. On admission to the hospital, at the age of 31, he was barely able to walk with canes. He had pronounced atrophy and weakness of the lower extremities, with ankle clonus, a Babinski sign and flexor spasms bilaterally. There was a sensory level at the eleventh thoracic dermatome. Lumbar puncture revealed partial block. Laminectomy in the lower thoracic area disclosed an extensive, infiltrating intramedullary oligodendroglioma of the spinal cord. The tumor was partially removed. The patient had complete paraplegia after operation.

Oligodendroglioma of the spinal cord is rare, only 6 other cases having been reported in the literature. The scoliosis in the present case is thought to have been produced by the tumor of the cord. The symptoms were of unusually long duration.

DISCUSSION

Dr. Percival Bailey: I have looked at the microscopic preparations, and, so far as I can judge, the tumor is an oligodendroglioma; its appearance, together with the course of the illness and the history, is compatible with such a diagnosis. This tumor is predominantly benign. The fact that the lesion in this case was not circumscribed but had infiltrated the cord makes the diagnosis more probable, since the ependymoma, the common glioma of the cord, is circumscribed. The only way of proving the nature of the tumor is to make silver impregnations, impossible in this instance because of insufficient tissue. The explanation of the scoliosis is probably correct; the fact that the muscles do not contract on one side causes the bones to be pulled out of position. It is apparent that it is useless to make bone grafts, as the grafts are also pulled out of line. Roentgen treatment is of little value.

Dr. Eric Oldberg: At the Neuropsychiatric Institute we have had a similar case, that of an adolescent girl, who was also treated for scoliosis by an orthopedist. She had an extensive astrocytoma and a block finally developed, for which operation was performed.

Dr. R. P. Mackay: Certain clinical features in this case suggest a much more extensive lesion than the tumor described. First, the scoliosis, if not a developmental anomaly, must have resulted from inequalities of muscle tone over a considerable area. Second, we were told that the patient had atrophy not only of the thighs, but also of the calves, a condition suggesting a lesion at a much lower level than the site of the tumor. I believe, therefore, that at autopsy one may expect to find syringomyelia, which is an extremely chronic developmental and proliferative

disease, frequently associated with a genuine neoplasm. The lesion in this case must be a very long one, occupying an area which the tumor (oligodendroglioma) could scarcely occupy.

Vertebral Angiography. Dr. Oscar Sugar, Dr. Lawrence B. Holden and Dr. Chester B. Powell.

A new percutaneous technic for vertebral arteriography is described. In essence, it consists of locating the vertebral artery as it passes from the transverse foramen of one cervical vertebra to the next. Properly timed roentgenograms made after injection of 20 cc. of iodopyracet injection U.S.P. (diodrast®) allow visualization of the arterial and venous circulations of the posterior half of the brain.

Four aneurysms of the basilar artery were found; these were pictured for the first time without operation. Metastases in the thalamus and the brain stem were discovered. Preoperative angiographic demonstration of acoustic tumor, pontile glioma and cerebellar hemangioblastoma was possible. Evidence supporting the diagnosis of basilar arteriosclerosis in a patient with a syndrome of the posterior inferior cerebellar artery was found by vertebral angiography. The procedure can also be used to determine the extent of the collateral cerebral circulation as in the case of a carotid–cavernous sinus fistula.

Vertebral angiography appears to be indicated in cases in which air study fails to visualize the posterior part of the third ventricle, the aqueduct of Sylvius and the fourth ventricle, and especially in cases in which exploration of the posterior fossa fails to reveal the cause of signs and symptoms which point to this region. The procedure requires general anesthesia but is well tolerated by patients with increased intracranial pressure; and it does not carry with it the necessity for operation which is found with air studies. It is, of course, valuable in the diagnosis of aneurysm when carotid angiography fails to reveal the source of subarachnoid hemorrhage; it can be carried out at the same angiographic session, for up to 120 cc. of iodopyracet (35 per cent) has been used in one session without difficulty. "Thorotrast" (a colloidal suspension of thorium dioxide) is used only if preoperative testing reveals sensitivity to the iodine-containing contrast medium. With the introduction of rapid-changing casettes, it should be possible to make a complete angiographic study of the cerebral circulation at one session without endangering the patient or the operator.

DISCUSSION

Dr. Harold C. Voris: Dr. Sugar and his colleagues are to be congratulated on the development of this technic. I have obtained vertebral angiograms unexpectedly on two occasions when attempting to make a percutaneous carotid angiogram, but I did not follow up with planned attempts to inject the vertebral arteries, perhaps because I felt that most, if not all, of the aneurysms in the posterior fossa are not amenable to surgical treatment, and that therefore vertebral angiograms would be only of diagnostic, and not of practical, value to the patient. This belief is obviously untenable, as Dr. Sugar has shown. I was especially impressed by his last point, the help in diagnosis afforded by ventriculograms which show internal hydrocephalus without air in the third ventricle but no definite evidence of tumor above the tentorium. This particular problem has long puzzled me, and often I do the wrong thing. I may make the diagnosis of tumor of the third ventricle when there is none, or, conversely, I may explore the posterior fossa when the tumor is not there. A procedure that will help the neurosurgeon in the

diagnosis of tumors of the midbrain or the posterior part of the third ventricle will be well worth while from that standpoint alone.

DR. PERCIVAL BAILEY: Moniz had the idea, but his arteriograms were all made by Almeida Lima. That is why he never developed the percutaneous method. Our stimulus came from a Japanese surgeon working at the Neuropsychiatric Institute, Dr. Kentaro Shimizu, now professor of surgery in the Imperial University, Tokyo. He told me last summer that he never attempted to puncture the vertebral artery between the transverse processes.

Perhaps it is of some interest to anatomists to see how clearly this injection outlines the thalamic distribution, which, of course, is the source of the thalamic syndrome.

DR. ERIC OLDBERG: Dr. Voris has already pointed out that diagnosis of these tumors is one of the greatest problems that confronts the neurosurgeon. Often air studies are not conclusive enough to inform the surgeon whether to approach through the posterior fossa or through the third ventricle.

Path of Distribution of Current in the Brain During Electric Convulsion Therapy. DR. F. M. LORIMER, DR. M. M. SEGAL and DR. S. N. STEIN.

This study attempts to indicate distribution through the brain of the electric current administered in electric convulsion therapy. A stereotaxic instrument is described which permits insertion of a rod carrying recording electrodes into the brain of a cadaver. After insertion of the rod, the recording electrodes can be ejected and spread to any amount desired. In these studies the electrode spacing used was 1.0 cm. The maximal potential drop between electrodes is sought out as the rod is rotated through a circle.

The experiment was designed to prove or disprove the theory that current travels in an "onion-shaped" field between shocking electrodes applied to the head. It is concluded that the current administered in electric convulsion therapy does not travel in a spindle-shaped pattern between the shocking electrodes, as it would in a homogeneous medium, but follows neural pathways.

Eric Oldberg, M.D., *President, in the Chair*
Regular Meeting, Feb. 8, 1949

Intramedullary Tumors of the Spinal Cord and Gliomas of the Intradural Filum Terminale. DR. HENRY W. WOLTMAN, Rochester, Minn.

An inquiry into what became of patients who had tumors of the kind designated revealed that intramedullary gliomas were not always incompatible with reasonably good health for many years, even when the tumor could not be removed, and that undue risk should not be taken in an attempt to remove a tumor that was not well encapsulated. Patients who had a tumor of the conus and filum terminale not only comprised the youngest group but also fared the worst. Patients who had an intramedullary ependymoma fared better than did those who had an intramedullary astrocytoma.

An attempt to correlate the activity of gliomas as established pathologically with the duration of the disease had to be abandoned because the number of malignant tumors was too small.

DISCUSSION

DR. JOSEPH A. LUHAN: I should like to ask whether postoperative roentgen therapy played any role in treatment and whether the results of irradiation were evaluated.

DR. PERCIVAL BAILEY: Some years ago I spent the summer with Professor Foerster at Breslau. He had a few intramedullary tumors which he wanted me to study, and I did so. I read all that I could find on the subject for the succeeding year and still did not exhaust the literature. That does not mean that the lesion is not rare; it is rare, as we all know, and probably no one has had as much experience with these tumors as Dr. Kernohan. I went to Rochester and studied his collection, and I still defer to his vast experience. I should like to know what criteria are used in defining the malignancy of an ependymoma.

DR. R. P. MACKAY: Can Dr. Woltman explain why tumors of the conus and filum terminale begin earlier, progress more rapidly and lead to disaster more quickly? There seems no a priori or theoretic reason that this should be true.

DR. HENRY W. WOLTMAN, Rochester, Minn.: I did not become interested in the possibilities of roentgen therapy for these patients until I had reviewed most of the histories; but it is something that Dr. Kernohan and I have talked about since, and something we should like to investigate further. I do not know whether it is possible in a small group of this kind to determine the value of roentgen therapy. One gets the impression that roentgen radiation may be helpful in some cases, even though the tumor is of a kind that presumably does not respond to irradiation.

Dr. Mackay asked a question that interests me. Of course, one does not know how long these patients have tumors before they produce symptoms; we know only how long they had symptoms before they went to the physician. The symptom of pain, for example, so common in the group with tumors of the filum terminale, may be tolerated longer than some symptoms, such as weakness or incontinence, that may be more alarming to the patient. I do not believe this explains why tumors of the conus are more rapidly progressive, though it may account for the difference of a year or so before the patient sees the physician. Patients with tumors of the conus come at a much earlier age than do those with intramedullary tumors situated at a higher level. It would seem that tumors of the conus begin to grow earlier than do the others. Possibly some of the pathologists can advise us on that.

Pathologic Features of Tumors of the Spinal Cord. DR. J. W. KERNOHAN, Rochester, Minn.

Histologically proved tumors of the spinal cord and its coverings were presented from three points of view: (1) their distribution at various levels of the spinal canal; (2) their location in relation to the spinal cord (intramedullary, extramedullary but intradural and, finally, extramedullary and extradural); (3) their gross and histologic nature. The commonest neoplasm in the spinal canal is the neurofibroma; the second in order of frequency is the meningioma, and the third, the intramedullary neoplasm. Most intramedullary neoplasms are gliomas, and of these the most frequent is the ependymoma. Neoplasms of the filum terminale are usually ependymomas.

Surgery of Intraspinal Lesions. DR. WINCHELL MCK. CRAIG, Rochester, Minn.

Since the first operation for the removal of an intraspinal tumor, many developments have taken place which have added to the facility of diagnosis and surgical treatment. Roentgen examination of the vertebral column, spinal puncture and examination of the cerebrospinal fluid, as well as myelography with use of gases or contrast mediums, have become necessary adjuncts to a careful neurologic

examination. Improvements in anesthesia, asepsis and refinements in surgical technic have increased the scope of surgery. Cooperation with the other surgical specialties, such as orthopedics, urology and plastic surgery, has been of great benefit in planning the approach to complicated problems involved in the surgical treatment of intraspinal lesions.

Eric Oldberg, M.D., *President, in the Chair*
Regular Meeting, April 12, 1949

Evolution of Neurologic Signs of Early Anterior Poliomyelitis. Dr. Irving C. Sherman and Dr. Eli L. Tigay.

Eleven neurologists were rotated in tours of duty day and night for thirty days in the Municipal Contagious Disease Hospital, Chicago. This plan resulted in many successive examinations of a small group of patients.

Data from 30 cases of poliomyelitis studied intensively showed that rigidity of the neck and the Brudzinski, Kernig and Lasègue signs appeared as in meningitis, but not so consistently or to such a severe degree. It is suggested that these signs are due to stretch pain. Weakness, when it appeared, did not progress steadily, but frequently fluctuated and finally terminated in paralysis or recovery. The same is true with regard to decrease in deep reflexes. The earlier and more persistent the absence of reflexes, the severer was the residual paralysis. Severe paralysis of the lower extremities was associated with early loss of abdominal reflexes in 85 per cent of examinations. There was no evidence of upper motor neuron lesions in our cases. Direct myotatic irritability was increased in muscles of the upper extremities oftener when they were paralyzed than when they were not paralyzed.

DISCUSSION

Dr. Oscar Sugar: Dr. Magoun, in a recent report on examination of the brain stem, stated that he had noted a large number of hemorrhagic lesions in the reticular formation, and he proposed these lesions as a possible cause of increased spasticity in anterior poliomyelitis. If such hemorrhages were present in these cases, it would explain how spasticity without the Babinski sign could exist. One must pay more attention to the reticular formation in the midbrain, for the pathways from here do not have anything to do with the Babinski sign.

Disturbance of Regulatory Mechanism of Sweating in Injuries of the Spinal Cord. Dr. Benjamin Boshes and Dr. Herman Blustein (by invitation).

The disturbance in sweat regulation after interruption of the spinal cord was studied in 26 patients with traumatic lesions of varying duration and severity. Thermoregulatory sweating can be cut off below complete lesions, anatomic or physiologic, but the distribution of preganglionic fibers from a given intact root may be so extensive as to reduce, or even eliminate entirely, any thermosweating loss. Drug or postganglionic sweating can survive any lesion of the cord and will persist even after postganglionic section provided that the sympathectomized area has a residual supply of parasympathetic, cholinergic nerves (vasodilator). The term "spinal reflex sweating" refers to pathologic sweating, which is seen best below complete or severe lesions of the cord. The mechanism may survive as long as ten years after injury. It may be found even when the spinal defense mechanisms, such as flexor spasms, are absent. The sympathetic nervous system, disconnected from the spinal cord at a given point, can survive, the longest period in our series being nine years.

DISCUSSION

DR. BENJAMIN BOSHES: I have only to point out that some of the sweating was asymmetric. The lesions, while anatomically leveled off, were physiologically asymmetric, so that there may sometimes be a Horner syndrome. The level of interruption was adaptable for our study.

Regulatory Disturbances of the Cardiovascular System in Injuries of the Spinal Cord. DR. HERMAN CHOR and DR. I. ZIVIN (by invitation).

When regulatory impulses from the cortex, diencephalon and medulla are interrupted by a transverse lesion of the cervical portion of the spinal cord, hypertension resulting from reflex stimulation by distention of the bladder or rectum and by cold and painful stimuli to the extremities is greater than in normal man. For the same reason, orthostatic hypotension is greater. Since in the case of a lesion of the cervical portion of the spinal cord sensory impulses from the upper extremities do not effect a connection with the cells of origin of the cervical sympathetic fibers, there is no rise of blood pressure in the upper extremity when the hand is stimulated by cold; on the other hand, sensory impulses from stimulation of the foot by cold do effect a connection, and the blood pressure rises. Because of the integrity of the glossopharyngeal-vagal reflex, the normal relations of increase in heart rate to lowered blood pressure and of decrease in heart rate to increased blood pressure are undisturbed with lesions of the spinal cord.

DISCUSSION

DR. FREDERICK HILLER: I have been particularly interested in this presentation, since I am not aware that similar observations on the spontaneous rise in the systemic blood pressure following transverse lesions of the spinal cord were made in the many cases of injury to the spinal cord during the first world war. No particular attention was paid to reflex changes in blood pressure on stimulation of the urinary bladder by distention. In fact, it has been stated that transections of the spinal cord, particularly at an upper thoracic or cervical level, are always followed by a drop in blood pressure. If, as we have been told, a reflex rise in blood pressure does occur after transverse lesions, the question arises whether this phenomenon is particularly noticeable after transverse lesions above the level of the fifth thoracic segment. In other words, can the rise in blood pressure be explained by excessive stimuli passing through the splanchnic nerves into the visceral arteries, causing their constriction, and hence a rise in blood pressure? Or is this vasomotor reflex due to stimulation of a cerebral vasomotor center, and does it use an extramedullary sympathetic reflex arc?

DR. OSCAR SUGAR: I cannot understand why in cases of lesion of the cervical level stimulation of the hand produces such a tremendous change in blood pressure, whereas stimulation of the leg causes no such change.

Spasticity, Pseudospontaneous Spasms and Other Reflex Activities Appearing Late After Injury to the Spinal Cord. DR. LEWIS J. POLLOCK and DR. BERNARD S. SCHAEFFER (by invitation).

Immediately after severe injury to the spinal cord a state of areflexia exists because of interruption of facilitory impulses from higher levels. Some time later primitive defense reflex mechanisms develop in the isolated distal segment of the spinal cord. These primitive patterns then change from simple withdrawal responses and flexor posture to the increasingly complicated movements observed

in pseudospontaneous spasms and in exteroceptive reflexes. The reflex response rarely consists of a simultaneous contraction of all participating muscles; rather, it is the result of successive reflexes elicited by a single stimulus. So-called spasticity is the resultant of many reflexes—stretch reflex, myotatic reflex, body reflexes and exteroceptive reflexes. The frequency of occurrence of paraplegia in flexion, spasticity, pluck reflexes, pseudospontaneous spasms and the potential total activity of the spinal cord is related to the level of the lesion, the incidence diminishing as lower segments are reached.

Eric Oldberg, M.D., *President, in the Chair*
Annual Meeting, May 10, 1949

Presidential Address: Neurosurgery and the Illinois State Hospital Program. DR. ERIC OLDBERG.

The development over the past eighteen years of the requirements for diagnostic and therapeutic neurosurgery on the part of the Illinois State Hospital System was reviewed. Once a simple matter, it is now greatly complicated by the introduction of diagnostic measures, such as angiography, and of therapeutic measures, such as lobotomy. Stock was taken of present facilities for handling the pressure of this load, and future plans for it was discussed.

Experimental Studies of Functional Recovery Following Repair of Nerve Defects with Fresh Homogenous Nerve Grafts. DR. LOYAL DAVIS and DR. DANIEL RUGE.

The use of plasma clot as a substitute for silk or tantalum sutures has gradually evolved in the past decade. An experimental study was made on cats in which homogenous grafts were placed with plasma. Comparisons were made with animals in which the grafts were sutured with silk. The animals were examined neurologically and by electrical stimulation. Histologic comparisons of the nerves were made. On the whole, the results of the plasma-placed grafts and the sutured grafts were identical.

DISCUSSION

DR. STANTON GOLDSTEIN: While it is agreed that end to end suture of severed nerves in man is the method of choice, there are times when this procedure is not feasible and the surgeon is confronted with the problem of bridging the defect. Autogenous nerve transplantation is generally accepted, but this procedure also is sometimes impossible. We believe that cable grafts are not practical, so the surgeon is faced with the possibility of using a homogenous nerve graft. Many investigators have tried and rejected this procedure with the idea that the graft produces a foreign body reaction and is reduced to a fibrous band or is absorbed entirely.

It is also said that the axis-cylinders do not grow through the graft and that recovery is impossible. However, in the past the patients have not been followed for long enough periods to justify conclusions regarding the efficacy of homogenous grafts. Under Dr. Davis' direction, homogenous nerve grafts have been performed on 11 patients who have been followed for longer periods, from six months to sixteen years. The grafts were taken from the sciatic nerves of recently amputated extremities or of cadavers shortly after death. They were obtained under strictly sterile precautions and were kept from thirty minutes to forty-five hours before being used. They were preserved under refrigeration but were not frozen.

While none of the patients has shown any notable return of function or enough evidence of regeneration for any approach to normal, some have shown minimal evidence of recovery. For 2 patients it is still too early to evaluate the results. Of the remaining 9 patients, 3 have shown minimal evidence of recovery, 1 has shown questionable evidence and 5 have shown no evidence.

Of those who have shown evidence of recovery, 1 patient had an injury to the peroneal nerve and two and a half years after transplantation of a homogenous nerve graft had perception of temperature and pinprick in the isolated sensory area of the peroneal nerve. Another patient had an injury to the radial nerve and fourteen months after nerve grafting was able to appreciate pain, touch, temperature and pressure in the isolated sensory area of the radial nerve. Neither of these patients had any demonstrable motor return. The third patient had a homogenous nerve graft of the median nerve, and three years later, although there was no recovery of sensory or motor function, there was definite electrical evidence of neurotization, as shown by a tetanus ratio of 4.4 and a practically level curve for repetitive stimulation.

One patient was admitted to the hospital about a year and a half after injury to the right tibial nerve, totally disabled because of a chronic ulcer of the heel. Although there has been no demonstrable return of motor or sensory function, there has been no recurrence of the ulcer in the sixteen years since the nerve grafting, and he has been able to carry on his work as a farmer with comfort.

A patient who was operated on less than a year ago has already begun to show evidence of return of sensation to the isolated sensory area of the radial nerve, and this bears out the point that sufficient time must elapse before one may judge whether or not there is any regeneration. However, if the effector mechanism is destroyed, no return of function can be expected, regardless of the procedure used.

A slide was shown of a graft 14.5 cm. long in place at the time of operation. The next slide showed a graft 11.5 cm. long in place one hundred and twenty-seven days after operation; the graft had retained its integrity in the host and had not been absorbed or reduced to a fibrous band. The microscopic pattern of the graft in the human nerve conforms to the description given by Dr. Ruge.

A Bowel Control Program in Cases of Injury of the Spinal Cord. DR. ISIDORE FINKELMAN and DR. H. J. LAWN.

In 91 per cent of 244 patients with injuries to the spinal cord a change from dependence on enemas to reflex defecation was effected. This freed the patients from dependence on assistance. It also averted the untoward effects of enemas, such as excessive sweating, nausea, spasm, weakness and black-outs. Reflex defecation may occur in a case of a complete lesion of the cauda equina and is apparently mediated by a local nerve plexus in the wall of the rectum. Stretching of the rectum or the presence of a mass is an adequate stimulus for contraction of the rectum and relaxation of the sphincter. The tonicity or flaccidity of the sphincter has no relation to successful development of reflex defecation. To change from use of enemas to reflex defecation may take only a few days. Enemas should be discarded early after injury. Although most of our patients came to us late after injury, we trained one of them to achieve reflex defecation three weeks after injury, and we have no doubt that this can be accomplished soon after the period of spinal shock. With the bowel control program in which enemas are dispensed with entirely, many man hours of attendance and large amounts of linen are saved. Patients develop much greater independence and confidence, and their morale and physical well-being are improved.

News and Comment

POSTGRADUATE COURSE IN CLINICAL NEUROLOGY

A postgraduate course in clinical neurology, designed to reorient the practicing physician in regard to the nervous system and the disease processes affecting it, will be given by the Department of Postgraduate Medicine, University of Michigan, Ann Arbor, May 8 to 11, 1950. The procedure of the neurologic examination will be reviewed, with special emphasis on some of the newer diagnostic procedures. Many of the manifestations referable to the nervous system more commonly met with in general practice will be discussed individually. Diagnostic procedures, differential diagnosis and the newer modes of therapeutic approach will be dealt with. The course will be augmented by clinical presentations and a review of the essential laboratory procedures. Further information may be obtained from Dr. Howard H. Cummings, chairman, Department of Postgraduate Medicine, University Hospital, Ann Arbor, Mich.

Book Reviews

Development of the Basic Rorschach Score, with Manual of Directions. By C. Buhler, K. Buhler and D. W. Lefever. Pp. ix plus 190. Los Angeles: Rorschach Standardization Studies, 1948.

The publication of this volume, the first in the series of "Rorschach Standardization Studies," by Buhler, Buhler and Lefever, is a real contribution to the field of Rorschach work. Although the study is essentially a statistical one, and will have most direct meaning to Rorschach workers familiar with statistics, it has importance for the clinical psychiatric and psychologic fields, both for its further objective, statistical examination of this widely used instrument and for the new technic—"the basic Rorschach score."

The study is a detailed statistical analysis of over 500 Rorschach records and in this respect is the first publication of its kind. The purpose of the study is to establish the degree to which the Rorschach technic can be quantified and standardized. In this volume there is presented a quantitative summary of the formal characteristics of this test, of meaning only to the Rorschach worker. More pertinent to the review is a comparison of determinants with clinical entities, such as the manic state and depression, for the investigation of psychodynamic forces which might be revealed through this projective technic. The manic state, as a state in which the superego is temporarily abolished, and depression, as a state in which the superego is severe, are used to study evidence for superego structure in the Rorschach test. The authors conclude that there is as yet no evidence for specific indicators of superego formation in the Rorschach test, but that the development of the superego must be evaluated from the general personality structure reconstructed from the protocol. The authors examine and confirm many of the concepts used by Klopfer.

Of more direct value in the psychiatric situation is the development of the basic Rorschach score. This was formulated in terms of the standard psychiatric diagnoses. Each patient was given a Rorschach test, and the psychiatric diagnosis was made on the basis of the clinical findings, whether the results of the Rorschach test agreed or not. The statistical formula was developed and the basic Rorschach scores were obtained for each subject. When these scores were graded, it was found that they agreed closely with the order of seriousness in which the psychiatrists had ranked the various clinical entities and that four levels of integration

or distintegration emerged: (1) adequacy, (2) conflict, (3) impairment and (4) loss of reality. "The four levels represent four degrees of reparable or irreparable loss of the personality's capacity to master conflict situations and to meet reality." This classification, if confirmed by further study, would provide a more objective evaluation of the depth of a patient's disturbance and thus eliminate some of the semantic confusion, as well as the uncertainty, which occurs in the estimation of treatment possibilities. It should be pointed out that interpretation of levels stops at this point. "It leads to analysis of the integration level, but does not aspire to specific diagnosing." It does, however, permit, in some situations, the possibility of ruling out suspected diagnoses when a score falls far from the score typical of one of the large groups. It must also be realized that only in a minor way can this estimate be used in the actual planning of the therapeutic approach.

Since the tables and figures are referred to only in a general way, it might have been more helpful if the tables had been placed in the appendix, as they tend to interrupt the reading for the many who are not statisticians. Although the book is mimeographed, rather than printed, it is an excellent publication.

MORTIMER M. MEYER, PH.D.

Dementia Praecox. The Past Decade's Work and Present Status: A Review and Evaluation. By Leopold Bellak. Price, $10. Pp. 456. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1948.

This book is based on a review of all the papers published on dementia precox, as listed in the *Quarterly Cumulative Index Medicus* for the ten year period from 1936 to 1946. In all, the bibliography consists of about 3,200 papers, in a variety of languages. In preparing this review, an abstract was made of each paper. This material was then organized in the form of the present book. The book, however, is not just a blackboard for recording work that has been done. An effort is made also to take stock of what the accumulated information seems to add up to.

The book comprises twenty chapters. There are chapters on etiology, pathogenesis and pathology, diagnosis and symptomatology, physiologic studies, psychologic studies, the shock therapies (five chapters), somatic therapies, psychotherapy, prognosis, complications, prevention and dementia precox in childhood. In each chapter the author presents brief abstracts of the papers which seem to him most pertinent, often with some comment as to the particular interest this paper seems to have. Each chapter closes with a brief summary of the material surveyed in the chapter and with a statement of the conclusions which the data seem to justify.

In the four pages of the final chapter, there is an admirable summary of the author's over-all conclusions. On the basis of the evidence recorded in the published literature, he states the belief that schizophrenia is a syndrome associated with a large variety of etiologic factors, rather than a disease entity with a single, yet to be isolated, etiologic agent. The best common denominator for this syndrome is a deficit reaction; i. e., "this syndrome is typical of a human organism incapable at the time of adequate social functioning." The etiologic factors may range from a hypothetically completely psychogenic nature to a hypothetically completely organic nature, with a continuum between these two hypothetic points and a given case occurring at some point on this continuum. In making a diagnosis in a given case, a consideration of the relative prominence of the following factors is recommended: (*a*) somatic predisposition, (*b*) sociopsychologic predisposition (together constituting schizophrenic reaction type liability), (*c*) psychologic precipitating causes, and (*d*) somatic precipitating causes. The suggestion is made that the term "schizophrenia" be used in those cases in which there are a minimum of somatic predisposition and of somatic precipitating causes and a maximum of sociopsychologic predisposition and of psychologic precipitating causes. The term "dementia precox," on the other hand, might be reserved for those cases in which there are a maximum of somatic

constitutional predisposition and precipitating causes and a minimum of socio-psychologic predisposition and precipitating causes. Such a differentiation seems justified by the results of prognostic studies. Cases with the best prognosis are those with a sudden onset of symptoms in a rather adequate prepsychotic personality, with precipitating factors present and with confusion, catatonic symptoms and some affective features prominent in the clinical picture. This syndrome has a better prognosis, with or without specific treatment, than the "dementia precox" syndrome, characterized by poor prepsychotic history and apparently constitutional characteristics of insidious onset in the presence of a clear sensorium and a conspicuous absence of any adequate affect.

The author notes that therapy constitutes one of the most controversial matters at present. He comments that the criteria for good prognosis are the same with or without shock treatment and that, in general, it seems that the shock treaments seem to improve the prognosis significantly in those cases in which the outlook is good anyway and may improve it in a proportion of those in which the outlook is ordinarily poor. These treatments seem to merit continued intensive investigation from all sides.

In reviewing the material for this book, the author was impressed by the fact that, usually, research is a by-product of busy clinicians occupied with daily routine problems who cannot help making their studies in a somewhat hit or miss fashion. He suggests that more research units, with opportunities for cooperative research, may be desirable for coordinated and more effective studies. The establishment of a clearing house, or central registry, for an orderly exchange and discussion of data is recommended. Increasing attention to a more careful experimental design in the setting up of investigative studies is suggested, with clear understanding of the concepts of significance of difference, validity, reliability and random selection. The need for an increased emphasis on objective criteria for diagnosis and prognosis, and particularly for appraisals of clinical status, is stressed.

This book attempts to mold into a comprehensible whole the cumbersome mass of diverse perspectives and investigations on the complex problem of dementia precox. It should be of particular use to the research worker, who inevitably becomes overattentive to the trees in his particular part of the forest, in filling in the contours beyond his habitual line of vision. It should also prove a useful guidebook to the physician with a general orientation on the schizophrenia problem who wishes to acquaint himself further with some of the more specialized aspects of this illness.

Medical Hypnosis. By Lewis R. Wolberg, M.D. Vol. I: The Principles of Hypnotherapy. Price, $5.50. Pp. 449. Vol. II: The Practice of Hypnotherapy. Price, $6.50. Pp. 513. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1948.

The first volume of this comprehensive work discusses the history, nature, technic and application of hypnosis, and the second volume, the use of hypnosis in short term psychotherapy.

Breuer and Freud discovered that hysterical patients under hypnosis revealed uneasy feelings associated with forgotten traumatic events and that the discharge of such feeling produced temporary relief. They then drew the conclusion that the hysterical symptoms corresponded to the abnormal direction of undischarged excitement (conversion). Freud clearly demonstrated the unconscious with hysterical patients under hypnosis; he uncovered feelings and memories for which there was no awareness in the conscious state. The carrying out after hypnosis of suggestions given during hypnosis allows of no other interpretation. Freud showed that repressed, unconscious feelings had a continuing dynamic effect on the personality. By the use of hypnotic suggestion the patient may discharge the emotional feelings unacceptable to his conscious self; but since the conscious self is, so to speak, not

present during hypnosis, it remains unchanged by the hypnotic remembering. In the conscious state the amnesia for the past still exists. The patient after certain hypnotic relief may again be confronted with situations which stir up the same unpleasant emotions. Since the patient must repudiate and repress these feelings because his conscious self is not desensitized to them, the hysterical symptoms will recur. Freud found that if he were to cure his patients permanently, the treatment must occur with the patient in full possession of his conscious critical faculties, yet able to face those unconscious feelings which he had repressed. As all know, after a brief period of experimentation with waking suggestion, Freud developed the method of free association.

Freud then threw into the discard hypnosis as an uncertain psychotherapeutic curative tool, whence it has been picked up by the author and by M. H. Erickson, Brenman, Gill, Kubie and others and polished to respectability. There is now no question that in the hands of experts hypnosis is a valuable adjunct to psychotherapy. It may be used as a catalyst to the various psychotherapies—material otherwise inaccessible for weeks and months may be unearthed and integrated quickly by suggestion, with the material of the waking state.

In these volumes by Dr. Wolberg, technics are described clearly and in great detail; the induction process is given step by step, and over and over. While this emphasis is tedious and adds to the length of the books, it focuses the picture clearly for the reader. The second volume contains transcriptions from illustrative cases exactly as they occurred, unpolished for publication and with all the colloquialisms of the consultation room. Despite the profusion of grammatical error, in some cases to the extent that meaning is obscured, the method is of extraordinary value to the physician who wants to learn technics. These interviews are so vivid that one easily puts oneself in the physician's place throughout the therapy; thereby learning may be facilitated.

While it is obvious that Dr. Wolberg is dynamically oriented in the psychiatric sense, he is catholic in his approach, utilizing concepts from many psychotherapeutic systems for the benefit of his patients. If the circumstances warrant, he tackles removal of symptoms with the same enthusiasm with which he undertakes the alteration of character. The treatment is flexible and runs the gamut of modern technics of hypnosis. The author utilizes experimental dreams with great facility, as well as regression to the age at which the traumatic events are presumed to have occurred; he creates artificial conflicts, sometimes involving himself, and uses automatic writing and drawing, imagery and dramatization, as in crystal gazing or the hallucinatory setting up of visually staged situations or the somnambulistic trance. The description of his methods is repetitive throughout and therefore should run less chance of misinterpretation. The author believes that free association is facilitated, buried memories are more readily recovered, dreams are clarified and resistance is overcome with hypnotherapeutic technics.

Dr. Wolberg wisely devotes a chapter to a discussion of the dangers, limitations and failures of hypnotherapy, indicating that they occur for the same reasons as failures with any type of psychotherapy. The reviewer believes it is on this chapter that the author rests his case. One closes these volumes with the thought that hypnosis handled by such experts in dynamic psychology and psychiatry as those named in the foregoing paragraphs will aid in the rehabilitation of some neurotic patients hardly approachable by other therapy.

In these volumes Dr. Wolberg surveys the fields of psychopathology, psychodynamics and psychotherapy. His work represents a contribution to the shortening technics of psychotherapy, so badly needed with the mushrooming growth of psychiatry. They are recommended to those wanting to know the principles and practice of hypnotherapy, with the reservation that it is to be devoutly hoped that such interest will be limited to experts in research and psychotherapy, and with the knowledge that of course no such thing will happen.

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